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The dimethyldiphenyls. By E. A. Johnson

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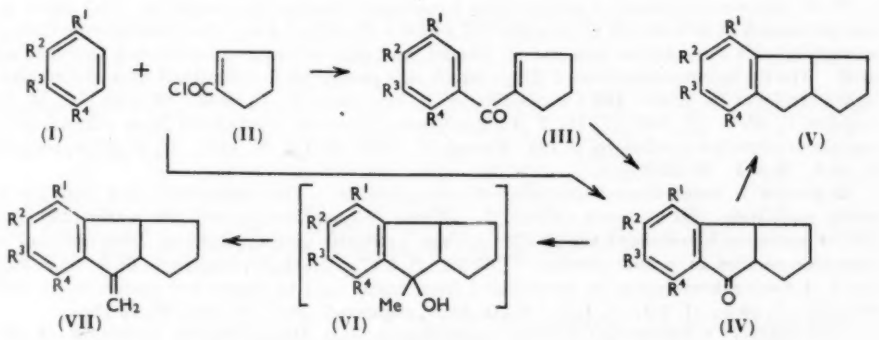
664. *Derivatives of* 1 : 2 : 3 : 3a : 8 : 8a-*Hexahydro*cyclo*pent*[a]*indene.*

By Alan Marchant.

Two methods for the synthesis of derivatives of 1 : 2 : 3 : 3*a* : 8 : 8*a*-hexahydro*cyclo*pent[*a*]indene are described.

Few derivatives of 1 : 2 : 3 : 3*a* : 8 : 8*a*-hexahydro*cyclo*pent[*a*]indene are known; the 3 : 3*a*-dihydroxy-1 : 2 : 3-triphenyl-derivative was reported by Ionescu and Popescu,[1] and the parent ketone (IV; $R^1 = R^2 = R^3 = R^4 = H$) has been prepared.[2]

The 5 : 6-dimethoxy-compound has now been prepared. 7-(3 : 4-Dimethoxyphenyl)-4 : 7-dioxoheptanoic acid with 2% potassium hydroxide solution underwent internal condensation to 2-(3 : 4-dimethoxyphenyl)-5-oxo*cyclo*pent-1-enylacetic acid, which, when heated with acetic anhydride, gave 5-acetoxy-7 : 8-dimethoxy-3-oxo*cyclo*penta[*a*]-naphthalene. Clemmensen reduction[3] in ethanol with granulated zinc gave 5-hydroxy-7 : 8-dimethoxy*cyclo*penta[*a*]naphthalene, which was oxidised by peracetic acid to 2-(2-carboxy*cyclo*pent-1-enyl)-4 : 5-dimethoxybenzoic acid. The acid obtained by hydrogenation of the double bond in the five-membered ring was cyclised by acetic anhydride to give the *cyclo*pentindene derivative (IV; $R^1 = R^4 = H$, $R^2 = R^3 = OMe$).



*cyclo*Pentene-1-carbonyl chloride (II) with benzene in the presence of 1 mol. of aluminium chloride at room temperature gives the *cyclo*pentenyl ketone (III; $R^1 = R^2 = R^3 = R^4 = H$), whilst at 80° with 3 mols. of aluminium chloride it undergoes further cyclisation to the *cyclo*pentindenone (IV; $R^1 = R^2 = R^3 = R^4 = H$). *cyclo*Pentene-1-carbonyl chloride (II) reacts similarly at 100° in the presence of 3 mols. of aluminium chloride with toluene, ethylbenzene, *o*-, *m*-, and *p*-xylene, veratrole, and *p*-dimethoxybenzene, to give ketones (IV). At 0° it reacts with anisole, to give ketone (III) but the methoxyl group is not stable to aluminium chloride at 100°.

Martin–Clemmensen reduction[4] of the carbonyl groups in these ketones gave the corresponding hexahydro-hydrocarbons (V). The ketones reacted with methylmagnesium iodide to give the corresponding 8-hydroxy-8-methyl compounds (VI), which were spontaneously dehydrated to the 8-methylene compounds (VII).

Structures have been assigned to the ketones (IV) by using the normal rules governing Friedel–Crafts reactions. Migration of the methyl groups, which might take place under

[1] Ionescu and Popescu, *Bull. Soc. chim. France*, 1932, 1215, 1231.
[2] Chatterjee, *J. Indian Chem. Soc.*, 1938, 211; Baker and Leeds, *J.*, 1948, 974; Baker and Jones, *J.*, 1951, 785.
[3] Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 846.
[4] Martin, *ibid.*, 1936, **58**, 1438.

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the drastic conditions of the reaction, is believed not to occur, since all the ketones distilled as homogeneous oils, which gave derivatives of differing, sharp melting points. For each ketone the carbonyl group gives a sharp infrared absorption band at different characteristic frequencies, which show a bathochromic shift depending on the number, type, and position of the substituents in the aromatic ring (cf. Table 1).

Experimental

3 : 4-Dimethoxy-α-furfurylideneacetophenone was prepared by Robinson's method.[5] Its **2 : 4-*dinitrophenylhydrazone*** crystallized from acetic acid in maroon needles, m. p. 170° (Found : C, 57·5; H, 4·0; N, 12·9. $C_{21}H_{18}O_7N_4$ requires C, 57·6; H, 4·1; N, 12·7%).

7-(3 : 4-*Dimethoxyphenyl*)-4 : 7-*dioxoheptanoic Acid*.—The foregoing ketone (90 g.), ethanol (900 g.), and concentrated hydrochloric acid (250 c.c.) were refluxed on the water-bath for 24 hr. The ethanol was evaporated and the residue refluxed for 3 hr. with concentrated hydrochloric acid (450 c.c.) and water (900 c.c.). The orange solution was decanted from the black oil. On cooling, the ***heptanoic acid*** (45 g.) crystallised. The mother liquors were used to re-extract the residual black oil by 2 hours' refluxing, and, when decanted and cooled, deposited more acid (22 g.). The acid crystallized from ethyl acetate in prismatic needles, m. p. 126° (Found : C, 61·0; H, 6·1. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·2%). Its ***bis*-2 : 4-*dinitrophenylhydrazone*** crystallized from ethyl acetate in vermilion needles, m. p. 244° (Found : C, 49·3; H, 4·1; N, 16·8. $C_{27}H_{26}O_{12}N_8$ requires C, 49·5; H, 4·0; N, 17·1%).

2-(3 : 4-*Dimethoxyphenyl*)-5-*oxo*cyclo*pent*-1-*enylacetic Acid*.—The heptanoic acid (30·7 g.) and potassium hydroxide (60 g.) in water (3 l.) were refluxed for 1 hr. Sodium chloride (150 g.) was added and the solution was cooled, filtered, and acidified with concentrated hydrochloric acid. The cyclo*pentenylacetic acid* (28 g.) which was precipitated crystallised from chloroform–light petroleum (b. p. 80—100°) in needles, m. p. 147° (Found : C, 64·85; H, 5·65. $C_{15}H_{16}O_5$ requires C, 65·1; H, 5·8%). Its **2 : 4-*dinitrophenylhydrazone*** crystallized from ethanol–ethyl acetate in vermilion needles, m. p. 185° (Found : C, 55·0; H, 4·3; N, 12·1. $C_{21}H_{20}O_8N_4$ requires C, 55·3; H, 4·4; N, 12·3%).

5-*Acetoxy*-7 : 8-*dimethoxy*-3-*oxo*cyclo*penta*[a]*naphthalene*.—The preceding acid (20 g.) in acetic anhydride (200 c.c.) was refluxed for 45 min., cooled, and poured into water (250 c.c.). The **4-*acetoxy*cyclo*pentanaphthalene*** (22 g.) was collected and crystallized from ethanol in colourless needles, m. p. 196° (Found : C, 67·97; H, 5·47. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). Its **2 : 4-*dinitrophenylhydrazone*** crystallized from acetic acid in bright red plates, m. p. 258° (Found : C, 59·6; H, 3·9; N, 12·0. $C_{23}H_{18}O_7N_4$ requires C, 59·7; H, 3·9; N, 12·1%).

5-*Hydroxy*-7 : 8-*dimethoxy*cyclo*penta*[a]*naphthalene*.—(*a*) Huang-Minlon reduction of this ketone gave a poor yield of 5-hydroxy-7 : 8-dimethoxy*cyclo*penta[*a*]naphthalene which crystallized from acetic acid in needles, m. p. 188°.

(*b*) The acetoxy-ketone (15 g.) in ethanol (500 c.c.) was refluxed with granulated zinc (75 g.) and concentrated hydrochloric acid (250 c.c.) was added in portions every hour for 7 hr. **5-*Hydroxy*-7 : 8-*dimethoxy*cyclo*penta*[a]*naphthalene*** (11 g., 88%) was precipitated. It crystallized from acetic acid in needles, m. p. 188° (Found : C, 73·97; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·5%).

2-(2-*Carboxyl*cyclo*pent*-1-*enyl*)-4 : 5-*dimethoxybenzoic Acid*.—5-Hydroxy-7 : 8-dimethoxy-*cyclo*penta[*a*]naphthalene (5 g.) in acetic acid (100 c.c.) was added during 3 hr. to a stirred acetic acid solution (40 c.c.; 11·5%) of peracetic acid at room temperature. The mixture was kept for 4 days. The pale yellow precipitate was then collected and washed with water and dried (2·0 g., 33%). The ***acid*** crystallized from benzene in colourless needles, m. p. 117° (Found : C, 61·5; H, 5·3. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%).

This acid (1·8 g.) was then reduced with 4% sodium amalgam (20 g.). **2-2′-*Carboxy*cyclo*pentyl*-4 : 5-*dimethoxybenzoic acid*** crystallized from benzene in needles, m. p. 160° (Found : C, 61·0; H, 6·1. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%).

1 : 2 : 3 : 3a : 8 : 8a-*Hexahydro*-5 : 6-*dimethoxy*cyclo*pent*[a]*inden*-8-*one*.—3 : 4-Dimethoxy-6-2′-carboxy*cyclo*pentylbenzoic acid (1·3 g.) in acetic anhydride (50 c.c.) was refluxed for 9 hr., cooled, and poured into water. Extraction with ether gave **1 : 2 : 3 : 3a : 8 : 8a-*hexahydro*-5 : 6-*dimethoxy*cyclo*pent*[a]*inden*-8-*one*** which crystallised from light petroleum (b. p. 40—60°)

[5] Robinson, *J.*, 1938, 1390.

in colourless prisms, m. p. 102° (0·5 g., 50%) (Found : C, 72·3; H, 7·0. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). Its 2 : 4-*dinitrophenylhydrazone* crystallized from acetic acid in deep red needles, m. p. 273° (Found : C, 58·0; H, 4·9; N, 13·9. $C_{20}H_{20}O_6N_4$ requires C, 58·2; H, 4·8; N, 13·6%), and its *oxime* from aqueous ethanol in colourless needles, m. p. 165° (Found : C, 67·8; H, 6·7; N, 5·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%).

1 : 2 : 3 : 3a : 8 : 8a-*Hexahydrocyclopent*[a]*inden*-8-*ones*.—(a) *General method*. *cyclo*Pentene-1-carbonyl chloride (1 mol.) in a large excess of the other reactant was treated, at 0°, with stirring, with aluminium chloride (3 mols.) during ½ hr., heated on the water-bath for 1 hr., kept at room temperature overnight, and poured on concentrated hydrochloric acid and ice, and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic material washed with sodium hydroxide solution and water and dried. After removal of the ether, the residue was distilled *in vacuo*. *Compounds* 1—6 (Table 1) were thus prepared.

(b) 4 : 7-*Dimethoxy-compound*. *cyclo*Pentene-1-carbonyl chloride (2·0 g.) and *p*-dimethoxybenzene (2·1 g.) in nitrobenzene (100 c.c.) were treated at 0° with aluminium chloride (6·5 g.) during ½ hr., heated for 1 hr. on the water-bath, left to stand at room temperature overnight, and poured on concentrated hydrochloric acid (25 c.c.) and ice. The nitrobenzene was removed in steam. The residue was extracted with ether, which was washed with sodium hydroxide and water, dried, and distilled, giving *compound* 7.

2 : 4-*Dinitrophenylhydrazones* (see Table 2) crystallized from acetic acid, *oximes* from aqueous ethanol.

TABLE 1. 1 : 2 : 3 : 3a : 8 : 8a-*Hexahydrocyclopent*[a]*inden*-8-*ones* (IV).

No.	R^1	R^2	R^3	R^4	Yield (%)	B. p./mm.	n_D^{20}	$\nu_{C=O}$ (μ)	Found (%) C	Found (%) H
1	H	Me	H	H	55	180—183°/12	1·5675	5·88	83·7	7·4 [d]
2	H	Me	Me	H	82	100—103°/0·1	1·5670	5·87	83·8	8·1 [e]
3	H	Me	H	Me	83	100—103°/0·1	1·5682	5·89	83·9	8·2 [e]
4	Me	H	H	Me	80	100—103°/0·1	1·5679	5·91	84·2	8·1 [e]
5	H	Et	H	H	80	130—133°/0·2	1·5558 [c]	5·88	84·3	8·2 [e]
6	H	OMe	OMe	H	60	205—207°/0·2 [a]	—	5·94	72·3	7·0 [f]
7	OMe	H	H	OMe	~18	204—206°/0·2 [b]	—	5·96	72·2	7·1 [f]

[a] M. p. 102°. [b] M. p. 132°. [c] At 24°. [d] $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%. [e] $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%. [f] $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%.

TABLE 2. *Derivatives of* 1 : 2 : 3 : 3a : 8 : 8a-*hexahydrocyclopent*[a]*inden*-8-*ones*.

No.[a]	M. p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
			2 : 4-*Dinitrophenylhydrazones* [b]					
1	193° [c]	62·1	5·0	15·2	$C_{19}H_{18}O_4N_4$	62·3	4·7	15·3
2	215 [d]	63·3	5·5	14·5	$C_{20}H_{20}O_4N_4$	63·2	5·4	14·7
3	231 [c]	63·4	5·8	14·6				
4	226 [c]	63·1	5·3	14·4				
5	205 [c]	63·0	5·1	14·6				
6	273 [c]	58·0	4·9	13·5	$C_{20}H_{20}O_6N_4$	58·2	4·8	13·6
7	263 [c]	57·9	4·5	13·6				
			Oximes [e]					
1	136	77·5	7·4	6·7	$C_{13}H_{15}ON$	77·6	7·5	7·0
2	148	78·0	7·9	6·3	$C_{14}H_{17}ON$	78·1	7·9	6·5
3	145	77·9	7·8	6·4				
4	144	78·2	8·0	6·2				
5	144	78·0	7·8	6·4				
6	165	67·8	6·7	5·7	$C_{14}H_{17}O_3N$	68·0	6·9	5·7
7	168	67·9	7·0	5·5				

[a] Nos. as in Table 1. [b] Red. [c] Needles. [d] Prisms. [e] Plates.

1 : 2 : 3 : 3a : 8 : 8a-*Hexahydrocyclopent*[a]*indenes*.—The *cyclo*pentindenone (1 g.) in toluene (10 c.c.) was added to amalgamated zinc (10 g.), concentrated hydrochloric acid (20 c.c.),

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and water (15 c.c.), stirred under reflux for 9 hr., concentrated hydrochloric acid (10 c.c.) being added every hour. After cooling, the toluene layer was separated, washed with aqueous sodium carbonate and water, dried, and evaporated. The residue was distilled *in vacuo*. The products are shown in Table 3.

p-*Anisoyl*cyclo*pentene*.—*cyclo*Pentene-1-carbonyl chloride (2·4 g.) in anisole (150 c.c.) was treated at 0°, with stirring, with aluminium chloride (7·5 g.) during ½ hr., left at room temperature for 24 hr., and poured on concentrated hydrochloric acid (50 c.c.) and ice. The anisole layer was separated and the aqueous layer extracted with ether. The combined extracts were washed with sodium hydroxide solution and water, dried, and evaporated. *Anisoyl*cyclo*pentene* (0·7 g., 19%) distilled at 145—148°/10·2 mm. and had n_D^{20} 1·5941 (Found: C, 77·5; H, 6·3. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%), having an infrared peak at 6·14 μ. This compound could not be cyclized under the conditions described above owing to demethylation by the aluminium chloride.

TABLE 3. 1 : 2 : 3 : 3a : 8 : 8a-*Hexahydro*cyclo*pent*[a]*indenes* (V).

No.	R¹	R²	R³	R⁴	Yield (%)	B. p./mm.	n_D^{20}	d_{24}^{24}	Found (%) C	Found (%) H
1	H	Me	H	H	82	126—128°/12	1·5363 [c]	0·9971	91·1	8·9 [e]
2	H	Me	Me	H	88	155—158°/12	1·5452	0·9980	90·5	10·0 [f]
3	H	Me	H	Me	83	154—157°/12	1·5471	0·9982	90·0	9·8 [f]
4	Me	H	H	Me	86	160—162°/12	1·5450	0·9979	90·0	8·6 [f]
5	H	Et	H	H	85	163—165°/12	1·5258 [d]	0·9987	90·1	10·0 [f]
6	H	OMe	OMe	H	80	150—151°/0·1 [a]	—	—	77·0	8·4 [g]
7	OMe	H	H	OMe	85	151—153°/0·15 [b]	—	—	77·1	8·1 [g]

[a] M. p. 37°. [b] M. p. 55°. [c] At 24°. [d] At 21°. [e] $C_{13}H_{16}$ requires C, 91·3; H, 8·7%. [f] $C_{14}H_{18}$ requires C, 90·3; H, 9·7%. [g] $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%.

1 : 2 : 3 : 3a : 8 : 8a-*Hexahydro*-8-*methylene*cyclo*pent*[a]*indenes*.—The hexahydro*cyclo*pent[*a*]-inden-8-ones in ether were added, dropwise with shaking at 0°, to methylmagnesium iodide (1 mol.) in ether, then kept at room temperature overnight. The mixture was poured on dilute hydrochloric acid, the ether layer was separated, washed with aqueous sodium carbonate and water, and evaporated, and the residue distilled. *Products* are shown in Table 4.

TABLE 4. 1 : 2 : 3 : 3a : 8 : 8a-*Hexahydro*-8-*methylene*cyclo*pent*[a]*indenes* (VII).

No.[a]	Yield (%)	B. p./mm.	n_D^{20}	d_{24}^{24}	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
1	82	155—158°/12	1·5520	0·9989	91·5	8·6	$C_{14}H_{16}$	91·3	8·7
2	83	170—172°/12	1·5542	0·9995	91·1	9·3	$C_{15}H_{18}$	90·9	9·1
3	83	172—174°/12	1·5580	0·9991	90·6	8·9			
4	92	168—171°/12	1·5570 [b]	0·9993	90·7	9·4			
5	75	173—175°/12	1·5481 [b]	0·9998	90·6	8·9			

[a] Nos. as in Table 1. [b] n_D^{24}.

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DYSON PERRINS LABORATORY, OXFORD. [*Received, November 16th,* 1955.]

665. *Alkali-metal–Amine Solutions. Spectroscopic and Magnetic Studies.*

By G. W. A. Fowles, W. R. McGregor, and M. C. R. Symons.

One or both of two intense electronic absorption bands in the visible and the infrared region, respectively, are invariably found in dilute solutions of alkali metals in amine solvents. Which band predominates and the precise position of the absorption maximum depend upon the solvent, the metal, and the temperature. Solutions showing only the visible band are not paramagnetic, whereas paramagnetism is found whenever the infrared band is detectable. In agreement with current theory, it is postulated that electrons are solvated, either singly or as pairs, and that the intense absorption band is caused by the transition of an electron to a discrete excited state defined by the solvent shell. Allocation of the visible and the infrared bands to excitations from paired and unpaired electrons respectively, and the factors affecting the pairing and unpairing of electrons, are discussed, together with the effect of changes in environment on the absorption maxima.

It has been established that alkali metals dissolve reversibly in liquid ammonia to give true, rather than colloidal, solutions. The precise nature of these solutions has been investigated in several ways. Conductivity studies [1] have shown that these solutions have an equivalent conductance greater than that found for any salt in liquid ammonia; in very dilute solutions the conductance is about three times that of a salt in liquid ammonia, while in concentrated solutions the conductance closely approaches that of a metal. These results have been interpreted as a dissociation of the metal atoms into metal ions and solvated electrons, $M \rightleftharpoons M^+ + e$, the high conductivity of the dilute solution being attributed to the abnormal mobility of solvated electrons. Further information on the nature of solvated electrons is provided by density measurements,[2] which show that solutions of metals are less dense than pure ammonia to the extent of at least 70 Å [3] per alkali-metal atom dissolved, and by measurements of magnetic susceptibility [3] and paramagnetic resonance absorption.[4] Magnetic measurements show that paramagnetic species are present at low concentrations, but that the solutions become increasingly diamagnetic as they become more concentrated, and that, further, the paramagnetism increases with increase in temperature. Since the characteristic spectra of the metal atoms cannot be detected, these changes in paramagnetism are generally attributed to the presence of electrons solvated either singly or in pairs. The metal atoms are completely ionised and the resulting cations and electrons are stabilised by solvation. If the electrons are separately solvated, they will be paramagnetic, whereas they will be diamagnetic if they are solvated in pairs.

In the model described by Kaplan and Kittel,[5] based on the investigations by Hutchinson *et al.*,[4] the solvated electrons exist in delocalised molecular orbitals on all the solvent protons surrounding cavities which the electrons create in the solvent. The molecular orbitals are described by a wave function of the type

$$\Psi = p^{-\frac{1}{2}} \sum_{i=1}^{p} \psi_i$$

where p is of the order of 50, and ψ_i represents the 1*s* atomic orbital on the ith proton together with a small contribution from higher-energy states. In an alternative

[1] Kraus, *J. Amer. Chem. Soc.*, 1921, **43**, 749.
[2] Lipscomb, *J. Chem. Phys.*, 1953, **21**, 52.
[3] Freed and Sugarman, *ibid.*, 1943, **11**, 354.
[4] Hutchinson and Pastor, *Rev. Mod. Phys.*, 1953, **25**, 285; *J. Chem. Phys.*, 1953, **21**, 1959; Hutchinson, *J. Phys. Chem.*, 1953, **57**, 546.
[5] Kaplan and Kittel, *J. Chem. Phys.*, 1953, **21**, 1429.

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description, Platzman [6] considers the electron to be bound in the lowest discrete state of the potential created by the oriented solvent molecules. In both these models, the solvated electron is quite independent of the cation.

Recently, Becker *et al.*[7] have suggested that no cavities exist, but that the electron is associated only with the protons of the solvent molecules orientated around the cation. Our results suggest that, although the cation influences the solvation of the electron, the extreme position proposed by Becker is unlikely in dilute solutions.

Spectra.—Examination of the available spectroscopic data [8–13] for dilute solutions of the alkali and alkaline-earth metals in ammonia, amines, and mixed solvents shows the presence of one or both of two characteristic and very intense electronic absorption bands, one in the visible (~6500 Å) and the other in the infrared (~15,000 Å) region. A less intense, but continuous, absorption is also found, starting at about 5500 Å and extending into the ultraviolet. Apparently, the only exception to this generalisation is found in the spectra of some solutions of potassium, where there is an absorption peak at about 8000 Å; this exception is discussed below. The existing data, together with the results obtained in the present study, are summarised in Table 1.

Nature of the Absorption.—The concept that one species is responsible for both bands can be discarded, since often only one band is detectable, whilst in other cases a change of temperature increases one band at the expense of the other—a fact which implies the presence of two different absorbing species in equilibrium. Thus three problems present themselves: (*a*) What is the nature of the absorbing species? (*b*) What is the change induced when light is absorbed? (*c*) What are the reasons for the marked effect of slight changes in environment on the relative amounts of each absorbing species and on the precise positions of the band maxima?

(*a*) Blade and Hodgins [10] attribute the existence of two bands to the variation in physical arrangement of the solvent molecules around the periphery of cavities containing single electrons, and suggest that with amines there are traps or cavities containing single electrons in which the hydrogen atoms of either amino-groups only or both amino- and hydrocarbon groups are oriented inwards. These are termed amine traps and aliphatic traps respectively. The 15,000 Å peak is then attributed to amine traps and the 6500 Å peak to aliphatic traps. This theory clearly cannot account for the appearance of the visible peak in ammonia solutions at low temperatures and high concentrations, and it is also difficult to see why all possible intermediate arrangements of N–H and N–Me groups around the cavity are not just as likely as the two extremes postulated. In any case, on the basis of Kaplan and Kittel's interpretation,[5] the orientation of N–Me bonds around the cavity could only mean that fewer protons are available to contribute to the delocalised molecular orbital, since C–H bonds would not be sufficiently polar for the hydrogen atoms to contribute appreciably.

Platzman and Frank [14] also only consider single solvated electrons, and propose that the observed absorption bands are part of a series of transitions. This theory, again, does not explain why when both bands are observed in one solution a change in temperature favours one at the expense of the other.

We suggest that, since magnetic studies [4] show that the energies of paired (e_2) or unpaired (e_1) solvated electrons are very similar, the most reasonable explanation of the two main bands is that they are caused by e_2 and e_1 species severally. The paramagnetic-resonance results obtained by Hutchinson and Pastor [4] for liquid-ammonia solutions, and

[6] Platzman, unpublished results, quoted in footnote to p. 423 of ref. 14.
[7] Becker, Landquist, and Alder, *J. Chem. Phys.*, 1956, **25**, 971.
[8] Gibson and Argo, *J. Amer. Chem. Soc.*, 1918, **40**, 1327.
[9] Vogt, *Naturwiss.*, 1948, **35**, 298.
[10] Blade and Hodgins, *Canad. J. Chem.*, 1955, **33**, 411.
[11] Jolly, U.S. Atomic Energy Comm. Nat. Sci. Foundation, Washington D.C., 1952, U.C.R.L. 2008, 3.
[12] Bosch, *Z. Physik*, 1954, **137**, 89.
[13] Hohlstein and Wannagat, *Z. anorg. Chem.*, 1956, **288**, 193.
[14] Platzman and Frank, *Z. Physik*, 1954, **138**, 411.

those obtained by us for solutions in methylamine, ethylenediamine, and propylenediamine (see Table 2) strongly suggest that the infrared band is a property of the e_1 species and the visible band of the e_2 species. Thus solutions which show only the visible band are not detectably paramagnetic, although the total metal concentration (*ca.* 10^{-3}M) would give an unpaired-electron concentration many hundreds of times greater than the minimum which

TABLE 1. *Absorption spectra of dilute solutions of metals in amine solvents.*

Solvent	Metal	Temp.*	Range investigated (Å)	Absorption max. (Å)	Comments †	Ref.
NH_3	Li	−65° to RT	4000—7500	—	A	8
	Li	—	4000—20,000	18,000	—	9
	Li	− 70	4000—20,000	14,900	T.	10
	Li	−253	4000—25,000	5850; 12,500	B	12
	Na	−65 to RT	4000—7500	—	A	8
	Na	—	4000—20,000	18,000	—	9
	Na	—	10,000—25,000	15,000	—	11
	Na	− 60	4000—20,000	14,700	T.	10
	Na	−253	4000—25,000	5900; 12,500	B	12
	K	−65 to RT	4000—7500	—	A	8
	K	−70	4000—20,000	15,000	—	10
	Mg	−65 to RT	4000—7500	—	A	8
	Ca	−65 to RT	4000—7500	—	A	8
$MeNH_2$	Li	−60	4000—20,000	13,500	—	10
	Li	—	4000—16,000	7100; 13,000	—	13
	Na	−60	4000—20,000	6400	—	10
	Na	−70 to RT	4000—7500	6500	—	8
	Na	—	4000—16,000	6900	—	13
	K	−60	4000—20,000	6540; 8200	—	10
	K	−70 to RT	4000—7500	6500	—	8
	Ca	−60	4000—20,000	12,800	—	10
$EtNH_2$	Li	−40	4000—20,000	14,200	—	10
	Li	—	4000—16,000	6800	—	13
	Na	—	4000—16,000	6800	—	13
	K	−60	4000—20,000	6450	—	10
$(\cdot CH_2\cdot NH_2)_2$	Na	RT	4000—10,000	6700	—	‡
	K	RT	4000—10,000	6700	—	‡
$NH_2\cdot CHMe\cdot CH_2\cdot NH_2$	Na	RT	4000—10,000	6600	—	‡
	K	RT	4000—10,000	6700	Also small shoulder at 8200 Å	‡
NH_3–$MeNH_2$						
(90—80% $MeNH_2$)	Li	—	4000—16,000	7400—7500; 13,000	—	13
(70% $MeNH_2$)	Li	—	,,	13,000	—	13
(90% $MeNH_2$) ...	Na	—	,,	7000	—	13
(80—70% $MeNH_2$)	Na	—	,,	7200; 13,200—12,500	—	13
(60—0% $MeNH_2$)	Na	—	,,	12,500—12,000	—	13
(50% $MeNH_2$) ...	Na	−70	4000—20,000	13,300	—	10
NH_3–$MeNH_2$ (50%)...	K	−60	4000—20,000	14,000	—	10
NH_3–$EtNH_2$						
(90—70% $EtNH_2$)	Li	—	4000—16,000	7000—7200; 13,000	—	13
(60% $EtNH_2$)	Li	—	,,	12,500	—	13
(90—80% $EtNH_2$)	Na	—	,,	7000	—	13
(70—60% $EtNH_2$)	Na	—	,,	7000—7500; 13,000	—	13
(50% $EtNH_2$)	Na	—	,,	12,500	—	13

* RT = room temperature. † A = absorption increases with temperature; B = thin films, concentrated; T = temperature-dependent. ‡ This paper.

can be detected. When both bands are observed, or only that in the infrared region, then paramagnetic resonance absorption is always found.

Support for this allocation of the visible and infrared bands to the e_2 and e_1 species is provided by the Hutchinson and Pastor's magnetic measurements of liquid-ammonia solutions, which show that e_2 is favoured as the temperature is lowered, while Blade and Hodgins [10] find that the visible band of a solution in a mixed ammonia–methylamine solvent is favoured at the expense of the infrared band at lower temperatures (thus agreeing with the qualitative observations by Ogg [15] on analogous solutions in liquid ammonia).

[15] Ogg, *J. Chem. Phys.*, 1946, **14**, 114.

(*b*) It is often stated (see, *e.g.*, ref. 5) that the intense absorption associated with solvated electrons corresponds to the total ejection of an electron from the cavity composed of orientated solvent molecules into bulk, unorientated solvent (described as a conduction band). Similar theories have been invoked to describe the intense ultraviolet absorption of halide ions. However, Platzman and Frank [14] recently suggested that the electron in the excited state of a halide ion is still held by the orientated solvent shell, though more weakly. Indeed, one would expect an absorption continuum rather than a discrete band for a process involving total electron ejection.

Evidence for the nature of the act of light absorption in metal solutions is provided by the irradiation experiments of Linschitz, Berry, and Schweitzer,[16] who found that, when lithium in a glass of mixed ether, *iso*pentane, trimethylamine, and methylamine was irradiated, the strong visible absorption band was lost. These authors found that the band was discharged only when light of wavelength less than 5400 Å was used for irradiation, although the maximum absorption was at 6000 Å. A general increase in absorption in the near-infrared region, with a broad maximum at 12,500 Å was also observed. Our qualitative observation that when a blue glass of propylenediamine containing dissolved sodium is irradiated the blue colour is greatly diminished but never quite lost is in agreement with the work of Linschitz *et al.*

We can hence conclude that the two main absorption bands do not correspond to the ejection of an electron (paired or unpaired) from its cavity into a conduction band, but rather to its excitation into a higher-energy orbital still within the same cavity. We further suppose that the continuum observed below about 5500 Å corresponds to the total ejection of the electron into a conduction band. When this electron is forced out of its cavity completely, it is unable to return to its original state because of the rigidity of the solvent, but once the glass is allowed to soften, the electron can create a new cavity, so that the original absorption band returns. When one electron has been ejected from an e_2 cavity, then an e_1 cavity in effect remains, thus accounting in part for the increase in the infrared band observed by Linschitz.

(*c*) *Effect of Environmental Changes on the* $2e_1 \rightleftharpoons e_2$ *Equilibrium.*—It is apparent from Table 1 and from the results on mixed solvents reported by Blade and Hodgins,[10] that quite small changes in temperature, concentration, and the nature of the metal and solvent readily affect the equilibrium $2e_1 \rightleftharpoons e_2$, so that e_1 and e_2 must have very similar energies. Lowering the temperature or raising the concentration clearly favours the e_2 form. Solvents with relatively high dielectric constants (*e.g.*, NH_3) appear to favour e_1 formation irrespective of the metal, but in amine solvents e_1 formation occurs only when the metal ions have a high surface-charge density. It is perhaps significant that lithium is much more soluble in amines than either sodium or potassium, and that lithium alone of these metals forms appreciable amounts of e_1 cavities in such solvents. These trends are consistent and suggest that in amine solvents ion-pair formation may take place, so that the metal ion is close to the solvated electron and has a noticeable influence upon the type of cavity formed.

We are unable to explain the absorption band at 8500 Å which appears in relatively concentrated solutions of potassium in methylamine and propylenediamine. Since the band is reproducible but occurs only in these two solvents, it is unlikely to be caused by impurities in the metal. The band appears at such short wavelengths that it can hardly be caused by e_1 transitions (shifted by the effect of the metal ion) and in any case paramagnetic-resonance measurements show that the concentration of e_1 species is extremely small.

Effect of Environmental Changes upon the Position of Maximum Absorption and Band Width.—The results reported by Blade and Hodgins [10] show that subtle changes in environment have a marked effect, not only on the pairing of electrons, but also upon the

[14] Linschitz, Berry, and Schweitzer, *J. Amer. Chem. Soc.*, 1954, **76**, 5833.

exact positions of maximum absorption and widths of both bands. The magnitude of the shift of maximum absorption does not give a direct measure of the change in energy of either the ground or the excited state, but of the change in energy of one in relation to the other. The various trends may be summarised: (*a*) Increase in temperature broadens the band and shifts it to longer wavelengths. For a given solvent, this effect is more pronounced for e_1 than e_2 bands. (*b*) Increase in concentration shifts the band to shorter wavelengths. This effect is more marked for e_2 than e_1 bands, and is greater in amine solvents than in ammonia. (*c*) Replacement of hydrogen atoms by methyl groups (*i.e.*, in amines) gives a shift to shorter wavelengths, and in mixed solvents the band lies between the two extremes. This gradual change indicates that in mixed solvents the hydrogen atoms of the N–H bonds of both amines and ammonia molecules can contribute directly to cavity formation.

The effects closely parallel those reported for the same changes in environment on the first absorption band of the solvated iodide ion.[17] If either the e_1 or the e_2 bands represented the complete ejection of an electron from a cavity then one might have expected a reversal in the direction of the spectral shifts compared with those for iodide, since the ground state of the solvated electron resembles the excited state of the iodide ion. Since, however, the effects are very similar, the postulate that the excited electron is still held within the e_1 or the e_2 cavity is given further support.

It has been noted that the e_2 band in amine solvents is far more sensitive to changes in concentration than is the e_1 band in ammonia. This can probably be attributed to the combined effect of the higher charge density per cavity and the lower dielectric constant of the amine solvent which makes ion-pair formation significant despite the low concentrations.

Experimental

Purification of Materials.—Sodium and potassium were purified by distillation *in vacuo* into tubes sealed at one end, a modified version of the technique described by Dostrovsky and Llewellyn [18] being used. The samples of the metals taken for the distillation were cut under light petroleum from the centre of larger pieces.

Anhydrous ethylenediamine and propylenediamine were placed over potassium hydroxide pellets for some days, and then distilled through a 3 ft. column packed with glass helices. The middle fraction from the distillation was treated with sodium wire, and then distilled *in vacuo* on to freshly distilled alkali metal (sodium for ethylenediamine, potassium for propylenediamine); a permanent blue coloration was taken as a criterion of dryness.

Methylamine. An aqueous solution (30% w/w) was run on to pellets of sodium hydroxide; the liberated methylamine was passed through a column of glass wool mixed with moist, freshly precipitated mercuric oxide to remove traces of ammonia [19] and collected in a trap cooled with liquid oxygen. The amine was dried *in vacuo* with freshly crushed barium oxide and finally metallic sodium.

Preparation and Stability of Alkali-metal Solutions in Ethylenediamine and Propylenediamine.—The apparatus shown in Fig. 1 was used for the preparation of the metal solutions. A tube containing purified sodium or potassium was placed in *D*, which was then sealed off, and the system was evacuated through the B14 joint, *J*, and well flamed to remove traces of adsorbed moisture on the walls. When gently heated, the metal ran through the constrictions c_1 and c_2 and solidified in *B*; a thin film of the metal was then distilled on to the walls of *A* and the constriction c_3 sealed off. The diamine was condensed into *A*, *via J*, and the apparatus was sealed off at constriction c_4, leaving the metal and amine in an all-glass, highly evacuated system containing no taps or joints liable to introduce impurities. The amine was allowed to warm to room temperature in contact with the metal, and the resulting solution was freed from excess of metal by filtration through the sinter *S* into *E*; the filtration was assisted by gently warming tube *A* (with the hand), thus slightly increasing the vapour pressure of the amine in this section.

[17] Smith and Symons, *J. Chem. Phys.*, 1956, **25**, 1074.
[18] Dostrovsky and Llewellyn, *J. Soc. Chem. Ind.*, 1949, **68**, 208.
[19] Hohlstein and Wannagat, *Z. anorg. Chem.*, 1956, **284**, 191.

XUM

Since lithium could not be melted through glass constrictions, a small portion of the metal was cut from the centre of a larger piece under light petroleum and while still wet with solvent was inserted into tube *A* against a counter-current of nitrogen; for this preparation, tube *D*

FIG. 1. *Apparatus for preparation of metal–diamine solutions.*

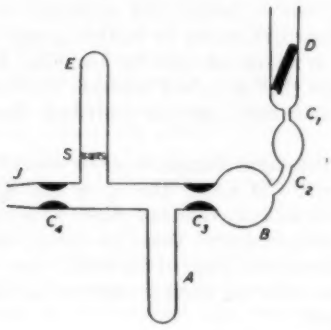


FIG. 2. *Apparatus for preparation of metal–diamine solutions for spectral studies.*

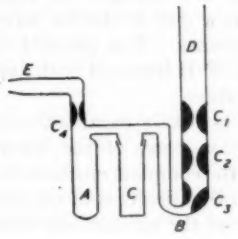
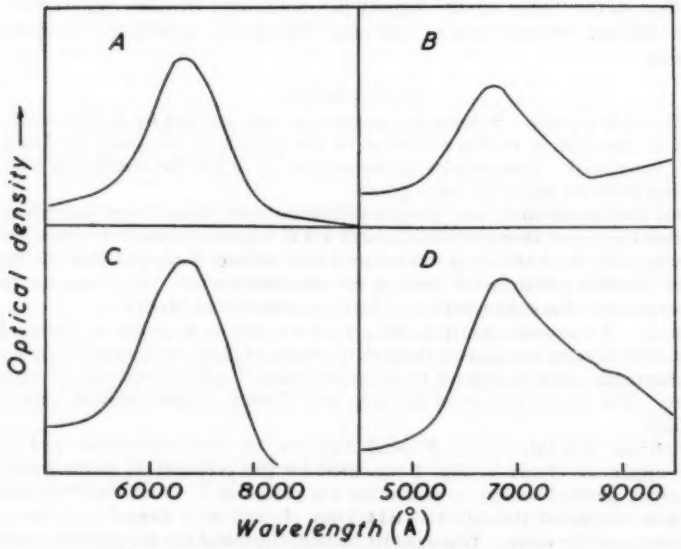


FIG. 3. *Absorption spectra.*



A, Sodium and, *B*, potassium in ethylenediamine.
C, Sodium and, *D*, potassium in propylenediamine.

and constrictions e_1, e_3, and e_2 were omitted from the apparatus. After evacuation, the solution was made up as before.

Sodium, potassium, and lithium gave blue solutions in both diamines. Several independent studies for each metal–amine combination showed that in both solvents sodium and potassium formed very much more stable solutions than did lithium. Thus sodium and potassium solutions generally decomposed over a period of 6—12 hr. while the lithium solutions were stable for only 15—30 min. The rapid decomposition of the lithium solutions can probably be attributed in part to impurities in the metal.

Effect of Metals on the Stability of the Solutions.—In the hope that conductivity measurements could be made over a range of concentration, the effect of possible electrode metals on the stability of the solutions was investigated. A small strip of electrode metal was sealed into a side arm on tube *E*, and after evacuation and flaming of the apparatus the blue solutions were prepared as before and tipped on to the metal strip. With molybdenum, tungsten, and platinum the colour decayed within a minute or two; in view of this, conductivity studies were not attempted.

It seems that these transition metals catalyse the decomposition of the metal–amine solutions because of their ability to accept electrons.

Strength of the Metal–Amine Solutions.—Precise measurement of the concentration of the metal in the solutions is difficult, since some decomposition to amide appears to be inevitable, and any determination of the metal concentration will give only the sum of the metal in solution and that present as amide. Any metal determination thus represents the maximum upper limit. The total concentration of sodium in a freshly prepared saturated solution in ethylenediamine was estimated on a calibrated flame-photometer, and found to be 0·02 g.-atom/per l.

A rough estimate of the concentration of metal in other solutions was then made by a comparison of the relative intensity of colour. On this basis, lithium is by far the most soluble of the alkali metals in either solvent; sodium and potassium in ethylenediamine and potassium in propylenediamine have similar solubilities, but sodium is only sparingly soluble in propylenediamine.

Absorption Spectra of Solutions of the Alkali Metals in Ethylenediamine and Propylenediamine.—Absorption spectra (3700—10,000 Å) were measured with a Unicam S.P. 600 spectrophotometer, the solutions being contained in fused silica cells (1 cm., equipped with standard C10 ground joints) which could be evacuated without distortion or breakage. Measurements below 3700 or above 10,000 Å were not reliable because of the strong absorption of the amine solvents. Unfortunately, cells thinner than 1 cm. could not be used, since they could not be evacuated and sealed.

The metal solutions were made in the apparatus shown in Fig. 2. The whole apparatus (except the cell *C*) was cleaned with hydrogen fluoride cleaning mixture [20] and dried for 12 hr. at 120°. The cell was cleaned with warm " Teepol," washed with pure acetone, and dried with warm air. The cell *C* was attached to the remainder of the apparatus with a trace of " Silicone " grease, and a tube of purified metal was placed in tube *D* which was then sealed. The whole apparatus was evacuated through joint *E*, and gently flamed (except cell *C*). After the apparatus had been pumped out for several hours, the metal was melted through constrictions c_1, c_2, and c_3 until a small globule appeared in *B*; the apparatus was then sealed at c_3. Sufficient solvent to fill cell *C* was then condensed in *A*, and the apparatus sealed at c_4; solvent was then carefully tipped into *C*, and its absorption compared with a " blank " cell containing boiled-out distilled water. A small portion of the solvent was tipped on to the globule of alkali metal in *B*, and the blue solution formed was carefully tipped back again into *C*. Gentle shaking gave a uniform dilute solution, whose absorption was again compared with the " blank " cell. The whole system, *A*, *B*, and *C* was designed to fit into a standard Unicam cell holder. All measurements were made at room temperature. The results for sodium and potassium in ethylenediamine and propylenediamine, shown graphically in Fig. 3, were obtained by subtracting the solvent absorption from that of the solution. Optical densities rather than extinction coefficients are recorded because of the difficulty of precisely estimating the concentration.

Paramagnetic Resonance Measurements on the Metal–Diamine Solutions.—The metal–diamine solutions were made in the usual manner, and tipped into a thin-walled Pyrex tube (3 mm.) so

TABLE 2. *Paramagnetic-resonance absorption in metal–amine solutions at room temperature (metal concentration about* 2×10^{-3}M).

Metal	Amine	Magnitude of absorption	Metal	Amine	Magnitude of absorption
Na ...	$(\cdot CH_2 \cdot NH_2)_2$	Nil	Li	$MeNH_2$	Strong
K	,,	Very weak	K	,,	Weak
Na ...	$NH_2 \cdot CHMe \cdot CH_2NH_2$	Nil			
K	,,	Nil			

attached to the preparative apparatus that it could be placed directly into an H_{012} 3 cm. wavelength rectangular resonant cavity for paramagnetic-resonance measurements. The results

[20] Crawley, *Chem. and Ind.*, 1953, 1205.

obtained are summarised in Table 2. Concentrations were varied between 10^{-2} and 10^{-4}M, as judged from the intensity of the colour, and any absorption was found to increase with concentration. Experiments with lithium in methylamine showed that absorption was readily detected even in 10^{-4}M-solutions.

Irradiation Experiments.—Rapid cooling of a fairly deep blue solution of sodium in propylenediamine gave a clear, uncracked glass, the blue colour being undiminished in intensity. When this glass, immersed in liquid oxygen contained in an unsilvered Dewar flask was irradiated with light from a tungsten-filament lamp, the colour was slowly bleached, until, after about 4 hours' irradiation, only a faint blue colour remained. The original, deeper blue colour reappeared immediately when the glass softened. Repetition gave similar results, showing that no overall decomposition was occurring.

Grateful acknowledgment is made to the Esso Petroleum Company for the award of a maintenance grant to W. R. M., to Mr. D. Austen and Dr. D. Ingram for making the paramagnetic-resonance measurements, and to Mr. M. Smith for valuable discussions.

THE UNIVERSITY, SOUTHAMPTON. [*Received, February 5th,* 1957.]

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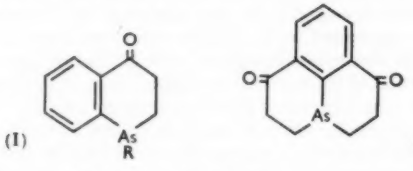
666. *The Synthesis and Properties of Substituted* 1 : 2 : 3 : 4-*Tetrahydro-4-oxoarsinolines and of* 1 : 6-*Dioxoarsulolidines.**

By FREDERICK G. MANN and A. J. WILKINSON.

Compounds having a keto- and a tertiary arsine group in one ring have been prepared for the first time. Cyclisation of 2-carboxyethyl-*m*-methoxyphenylmethylarsine gives 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline, and double cyclisation of di-(2-carboxyethyl)-*m*-methoxyphenylarsine affords 7-methoxy-1 : 6-dioxoarsulolidine, which is the first known compound in which two fused rings have one tervalent arsenic atom in common. The properties of these oxo-arsines have been investigated.

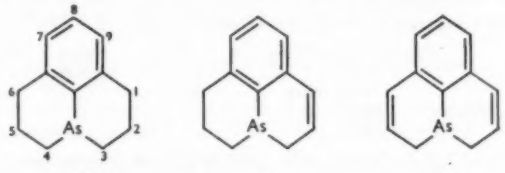
FOR the work described in the following paper, cyclic keto-arsines such as a 1-substituted 1 : 2 : 3 : 4-tetrahydro-4-oxoarsinoline (I) or 1 : 6-dioxoarsulolidine (II) were required.



(I) (II)

Compounds of this type containing a tertiary arsine group and a keto-group in one ring were unknown. Cookson and Mann [1] had attempted to cyclise 2-carboxyethyldiphenylarsine, $Ph_2As{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, and also the chloride, $Ph_2As{\cdot}CH_2{\cdot}CH_2{\cdot}COCl$, to form

* Following the Editor's advice, the term arsulolidine is applied to the structure (A), in harmony with its nitrogen analogue julolidine. The systems (B) and (C) would thus be arsuloline and arsuline respectively (cf. *J.*, 1951, 1898).



(A) (B) (C)

[1] R. C. Cookson and Mann, *J.*, 1949, 67.

1 : 2 : 3 : 4-tetrahydro-4-oxo-1-phenylarsinoline (I; R = Ph) but without success. They failed also to convert di-(2-carboxyethyl)phenylarsine, $Ph{\cdot}As(CH_2{\cdot}CH_2{\cdot}CO_2H)_2$, by a double cyclisation into 1 : 6-dioxoarsulolidine (II).

In an attempt to prepare the 1-methyl-oxo-arsine (I; R = Me), dichlorophenylarsine, $Ph{\cdot}AsCl_2$, was converted by a Meyer reaction using aqueous sodium hydroxide and methyl sulphate into methylphenylarsinic acid [2] (III), which on reduction with amalgamated zinc

$$\underset{\text{(III)}}{PhMeAsO{\cdot}OH} \longrightarrow \underset{\text{(IV)}}{PhMeAsH} \longrightarrow \underset{\text{(V)}}{PhMeAs{\cdot}CH_2{\cdot}CH_2{\cdot}CN} \longrightarrow \underset{\text{(VI)}}{PhMeAs{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}$$

dust and concentrated hydrochloric acid at room temperature [3,4] gave methylphenylarsine (IV). This arsine readily reacted with vinyl cyanide to give 2-cyanoethylmethylphenylarsine (V), in accordance with the experience of Cookson and Mann [1,4] who found that an alkaline catalyst, although exerting a powerful effect on the cyanoethylation of arsines, was seldom necessary. Hydrolysis then gave 2-carboxyethylmethylphenylarsine (VI).

The arsenic atom in the liquid cyanoethylarsine (V) shows, although to a smaller extent, the partial deactivation shown by that in 2-cyanoethyldiphenylarsine, $Ph_2As{\cdot}CH_2{\cdot}CH_2{\cdot}CN$. Thus the arsine (V) is quaternised with cold methyl iodide, and by warm methyl toluene-*p*-sulphonate: the methiodide however readily loses methyl iodide. The arsine is converted into the arsine oxide by hydrogen peroxide in acetone, but is only slowly affected by air at room temperature: in this respect it is intermediate between dimethylphenylarsine, which is readily oxidised, and di-(2-cyanoethyl)phenylarsine, which is stable indefinitely in air.[4]

Attempts to cyclise the nitrile (V) failed. This was not unexpected, for the only method known for the cyclisation of the analogous *N*-2-cyanoethyl-*N*-methylaniline [5] entails heating with a mixture of aluminium chloride, sodium chloride, and potassium chloride under strictly controlled conditions of time and temperature. The application of this mixture to the nitrile-arsine (V) would probably cause rapid co-ordination of the aluminium chloride with the tertiary arsine, with additional deactivation of the benzene ring.

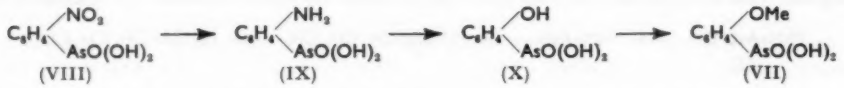
Cyclisation of the acid (VI) was unsuccessfully attempted by heating the acid (*a*) with phosphoric anhydride suspended in xylene or dissolved in syrupy phosphoric acid, and (*b*) with concentrated sulphuric acid. The acid chloride, when heated with aluminium chloride in various solvents, gave only non-ketonic tars.

These results indicated strongly that activation of the benzene ring by a suitable substituent was necessary to achieve cyclisation. To obtain maximum effect for this purpose, *m*-methoxyphenylarsonic acid (VII) was required. Several routes were available for its preparation. *m*-Anisidine, when subjected to the Bart reaction, gave the acid (VII) in only 22% yield (low yields in this reaction being often obtained with *m*-substituted anilines), and the anisidine is costly to buy and tedious to make. Alternatively, *m*-nitroaniline, which also gives very low yields when subjected to the normal Bart reaction, was converted into *m*-nitrophenylarsonic acid (VIII) in 57% yield by using Doak's application [7] of Scheller's modification [8] of the Bart reaction, in which diazotisation is carried out in ethanol and the diazonium salt is coupled with arsenic trichloride in the presence of a cuprous catalyst, hydrolysis then giving the acid (VIII). In view of the consistent yields thus obtained, direct nitration of phenylarsonic acid was not attempted. The acid

[2] Cragoe, Andres, Coles, Elpern, Morgan, and Hamilton, *J. Amer. Chem. Soc.*, 1947, **69**, 929.
[3] Palmer and Adams, *ibid.*, 1922, **44**, 1362.
[4] R. C. Cookson and Mann, *J.*, 1947, 618.
[5] Allison, Braunholtz, and Mann, *J.*, 1954, 403; cf. also F.P. 806,715/1936.
[6] Hamilton and Morgan, "The Bart, Béchamp and Rosenmund Reactions" in "Organic Reactions," Vol. II, p. 415, Wiley, New York, 1944.
[7] Doak, *J. Amer. Chem. Soc.*, 1940, **62**, 167.
[8] Scheller, B.P. 261,026/1925; F.P. 624,028/1926.

XUM

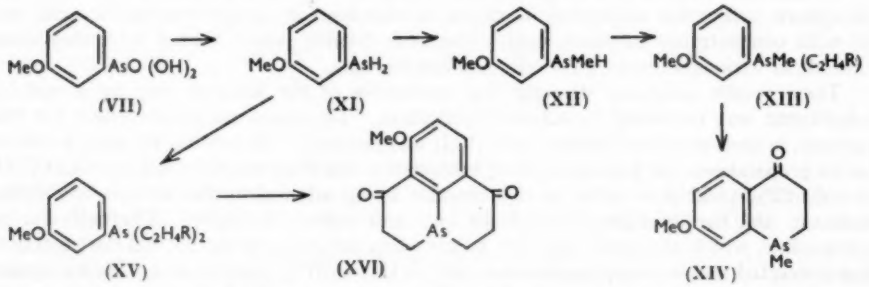
(VIII) was then reduced by Rozina's method[9] to *m*-aminophenylarsonic acid (*m*-arsanilic acid) (IX), which after diazotisation gave *m*-hydroxyphenylarsonic acid (X). This acid is very soluble in water, however, and therefore without isolation it was methylated directly in alkaline solution with methyl sulphate to give the much less soluble methoxy-acid (VII).



(VIII) (IX) (X) (VII)

Two methods were available for the next stage, namely, the conversion of *m*-methoxyphenylarsonic acid (VII) into *m*-methoxyphenylmethylarsine (XII). The acid (VII) could be reduced to dichloro-*m*-methoxyphenylarsine, which by a Meyer reaction with methyl sulphate and alkali should furnish *m*-methoxyphenylmethylarsinic acid, MeO·C_6H_4·AsMe(:O)·OH, the reduction of which would give the arsine (XII). This method was long and, in view of the low yields obtained in the comparable reduction of methylphenylarsinic acid, it was not investigated. Alternatively, the acid (VII) was reduced in good yield to *m*-methoxyphenylarsine (XI), which was converted into the methylarsine (XII) by Mann and Smith's method,[10] the arsine in liquid ammonia being converted first into *m*-methoxyphenylsodioarsine by the addition of one equivalent of sodium, and then into the methylarsine (XIII) by the action of methyl iodide. The sharp colour changes which accompany each of these stages are of considerable help in this preparation. It is noteworthy that the reported cleavage[11] of alkyl aryl ethers by sodium in liquid ammonia was apparently completely absent during the above reactions, probably because of their great rapidity.

The arsine (XII) was readily converted by vinyl cyanide into the liquid 2-cyanoethyl-*m*-methoxyphenylmethylarsine (XIII; R = CN), which on alkaline hydrolysis gave 2-carboxyethyl-*m*-methoxyphenylmethylarsine (XIII; R = CO_2H). Both these compounds gave methiodides at room temperature, but were stable indefinitely in air: the combined inductive effects of the *m*-methoxyl group and the cyano- or carboxylic group deactivated the tertiary arsine group sufficiently to prevent atmospheric oxidation.



(VII) (XI) (XII) (XIII)
(XV) (XVI) (XIV)

No attempt was made to cyclise the nitrile (XIII; R = CN). The acid (XIII; R = CO_2H) however, when heated in boiling xylene for 2 hours with phosphoric anhydride and " Hyflo Supercel," gave the colourless crystalline 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline (XIV) in 35% yield.

It is of interest that this is only the second recorded example of the formation of a cyclic arsine system by the establishment of a carbon–carbon bond, the first being Das Gupta's claim that chloro-2-chlorovinylphenylarsine, Ph·AsCl(CH:CHCl), undergoes an

[9] Rozina, *Zhur. priklad. Khim.*, 1950, **23**, 1110; see also Mann and Stewart, *J.*, 1954, 4127.
[10] Mann and Smith, *J.*, 1952, 4544.
[11] Birch, *J.*, 1944, 430; 1947, 102.

internal Friedel–Crafts reaction to give 1-chloroarsindole.[12] All other such cyclisations have involved, directly or indirectly, the formation of a carbon–arsenic bond, as in Burrows and Turner's initial synthesis of the parent 1 : 2 : 3 : 4-tetrahydro-1-methylarsinoline by the cyclisation of chloro-methyl-3-phenylpropylarsine.[13]

The fact that the methoxy-group in the arsinoline (XIV) is in the 7- and not the 5-position is clearly shown by the infrared spectrum. This shows a strong band at 12·04 μ and none in the 12·75—13·5 μ region : 1 : 2 : 4- and 1 : 2 : 3-trisubstituted benzenes have a well-defined band at 12·2 and 13·1 μ respectively.

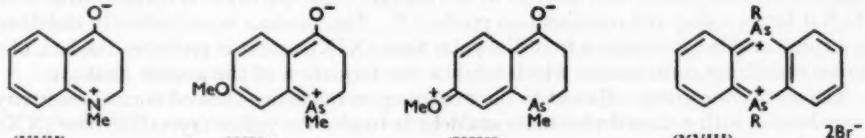
m-Methoxyphenylarsine (XI), when heated with an excess of vinyl cyanide in nitrogen, readily underwent dicyanoethylation to give di-(2-cyanoethyl)-*m*-methoxyphenylarsine (XV; R = CN), which on prolonged alkaline hydrolysis gave the crystalline di-(2-carboxyethyl)-*m*-methoxyphenylarsine (XV; R = CO_2H). Both these compounds are stable indefinitely in the air; the acid readily gave a methiodide at room temperature.

The acid (XV; R = CO_2H), when boiled with phosphoric anhydride in toluene, xylene, or benzene, underwent dicyclisation, forming the highly crystalline 7-methoxy-1 : 6-dioxoarsulolidine (XVI). A number of experiments showed that the maximum yield (11%) was obtained in toluene with only 15 minutes' boiling: in xylene consistently lower yields were obtained, whilst in benzene the dicyclisation was very slow. The acid (XV; R = CO_2H), when heated with a mixture of phosphoric anhydride and syrupy phosphoric acid, also gave the diketone (XVI) in inferior yield, together with an alkali-soluble ketonic gum which was almost certainly 1-(2-carboxyethyl)-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxoarsinoline. This production of the diketone and the keto-acid is analogous to the results of Braunholtz and Mann,[14] who showed that the cyclisation of various *NN*-di-(2-cyanoethyl)anilines gave a mixture of the corresponding 1 : 6-dioxojulolidine and the 1-(2-cyanoethyl)-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline.

It is noteworthy that the arsulolidine (XVI) is the first known compound in which two fused rings have one tervalent arsenic atom in common.

The physical and chemical properties of the oxo-arsine (XIV) and the dioxo-arsine (XVI) will be discussed in turn, omitting reactions which involve the ketomethylene grouping and are discussed in detail in the following paper.

The colourless oxo-arsine (XIV) contrasts markedly with the yellow liquid 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline. The presence of the methoxyl group in the former prevents a strict comparison of the ultraviolet spectra of the two compounds. However, the effect of a methoxyl substituent on benzenoid absorption is usually to cause a shift to longer wavelengths with intensification of the maxima, without greatly altering the general form of the spectrum. The two spectra (Fig. 1) are in fact quite different. Most striking is the complete absence in the spectrum of the oxo-arsine (XIV) of the broad band with a maximum at 384 mμ which is responsible for the yellow colour of the oxo-amine. This absence undoubtedly indicates that whereas the polar form (XVII) makes an appreciable contribution to the oxo-amine, a similar form (XIVA) makes no contribution



(XVII) (XIVA) (XIVB) (XVIII)

to the oxo-arsine (XIV). The absence of the polar form (XIVA) is to be expected, for it is exceedingly rare for an arsenic atom in a ring to be linked to two ring carbon atoms by a single and a double bond respectively. This structure almost certainly exists in the

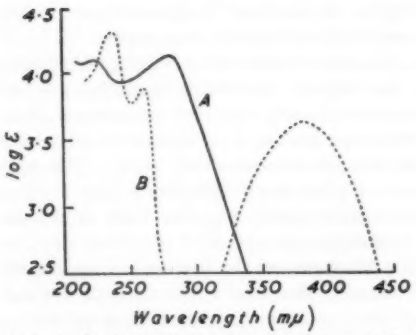
[12] Das Gupta, *J. Indian Chem. Soc.*, 1935, **12**, 627; 1937, **14**, 231.
[13] Burrows and Turner, *J.*, 1921, **119**, 426.
[14] Braunholtz and Mann, *J.*, 1953, 1817; 1954, 651.

5 : 10-dihydroarsanthronium dibromides (XVIII) [15] where it is stabilised by resonance, and it has been claimed (on insufficient evidence) for arsanthren [16] and phenarsazine.[17]

It is of interest that in the infrared spectra of the oxo-arsine and oxo-amine, the carbonyl group appears as a band at 6·05 and 5·97 μ respectively: for comparison, in *o*- and *p*-methoxyacetophenone, this band appears at 6·05 and 6·03 μ respectively.[18] The strong evidence for conjugation of the carbonyl group in the oxo-amine compared with that in the oxo-arsine, which is shown by the ultraviolet spectra, is therefore not shown by the infrared spectra.

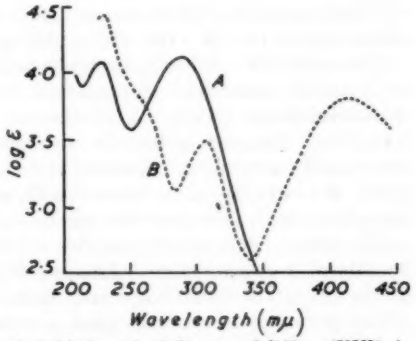
It should be added that the polar form (XIVB) of the oxo-arsine must also make only

FIG. 1.



A, 1 : 2 : 3 : 4-*Tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline* (XIV) *in ethanol.*
B, 1 : 2 : 3 : 4-*Tetrahydro-1-methyl-4-oxoquinoline in ethanol*: there is a minimum at 289 mμ (log ε, 1·74) not shown in the Figure.

FIG. 2.



A, 7-*Methoxy*-1 : 6-*dioxoarsulolidine* (XVI) *in ethanol.*
B, 1 : 6-*Dioxojulolidine in ethanol.*

a negligible contribution to the structure, otherwise it also would cause the oxo-arsine to be coloured. This factor applies also to the colourless *o*- and *p*-methoxyacetophenone.

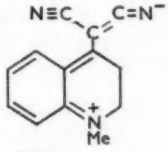
The oxo-arsine (XIV) undergoes ready quaternisation at room temperature, but appears to be stable indefinitely in air, in contrast to 1 : 2 : 3 : 4-tetrahydro-1-methylarsinoline which is slowly oxidised.[13]

The carbonyl group in the oxo-arsine (XIV) has normal reactivity in that it gives a phenylhydrazone and a semicarbazone. On the other hand, it could not be induced to react under a wide variety of conditions with a number of compounds containing " reactive" methyl or methylene groups, such as quinaldine methiodide, Fischer's base (1 : 3 : 3-trimethyl-2-methyleneindoline), 2-methyl-4 : 5-diphenylthiazole ethiodide, 2 : 3 : 6-trimethylbenzothiazole ethiodide, or malononitrile. 1 : 2 : 3 : 4-Tetrahydro-1-methyl-4-oxoquinoline shows a similar inertness to these reagents [19] except towards malononitrile with which it forms a deep red condensation product.[20] This product is undoubtedly stabilised by a considerable contribution from the polar form (XIX), and it is probably the lack of a similar stabilising contribution which inhibits the formation of the arsenic analogue.

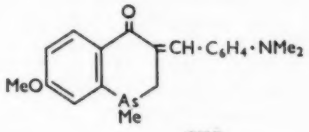
The methylene group adjacent to the oxo-group in the arsine showed normal reactivity in condensing with *p*-dimethylaminobenzaldehyde to give the yellow crystalline base (XX), and with *p*-nitrosodimethylaniline to give an anil, which however could not be obtained pure.

[15] Chatt and Mann, *J.*, 1940, 1184; Emrys R. H. Jones and Mann, *J.*, 1955, 411.
[16] Kalb, *Annalen*, 1921, **423**, 39.
[17] Wieland and Rheinheimer, *ibid.*, p. 1.
[18] Hergert and Kurth, *J. Amer. Chem. Soc.*, 1953, **75**, 1622.
[19] Ittyerah and Mann, unpublished work.
[20] Ittyerah and Mann, *J.*, 1956, 3179.

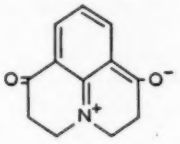
The colourless nature of 7-methoxy-1 : 6-dioxoarsulolidine (XVI) is also in contrast to the yellow colour of the nitrogen analogue, 1 : 6-dioxojulolidine, and undoubtedly the difference is again due to the absence in the dioxo-arsine (XVI) of any contribution similar to the polar form (XXI) of the dioxo-amine. The difference in their ultraviolet spectra in ethanol is shown in Fig. 2. The infrared spectrum of the dioxo-arsine shows two carbonyl bands at 5·85 and 5·98 μ, due undoubtedly to the greater influence of the methoxyl group on the neighbouring carbonyl group than upon the more distant one. The symmetric



(XIX)



(XX)



(XXI)

dioxo-amine shows only one carbonyl band at 5·97 μ. This difference in the carbonyl groups of the dioxo-arsine (XVI) is further shown by the fact that although both, for example, will form phenylhydrazones, one group is more reactive than the other in such condensations.

The dioxo-arsine (XVI) is unaffected by air at room temperature, and by boiling methyl iodide. The fact that 1 : 6-dioxojulolidine is also unaffected by methyl iodide could be attributed to considerable deactivation of the nitrogen atom by the polar contribution (XXI), a factor apparently absent from the dioxo-arsine. It is probable however that in these compounds the nitrogen and the arsenic atom are sufficiently rigidly held in the dicyclic system to make attainment of a tetrahedral configuration, which would accompany quaternisation, exceedingly difficult.

The dioxo-arsine could not be condensed with *p*-dimethylaminobenzaldehyde or with *p*-nitrosodimethylaniline.

Experimental

All compounds were colourless unless otherwise described.

Methylphenylarsinic acid (III) was prepared in 87% yield by the recorded method.[3]

Methylphenylarsine (IV).—A round-bottomed flask was fitted with a 3-necked adapter carrying a dropping-funnel, an inlet tube for nitrogen, and a reflux water-condenser, which in turn had a long air-condenser loosely plugged with cotton-wool to retard inward diffusion of air. Zinc dust (200 g.) was added in small portions with shaking to a solution of mercuric chloride (8 g.) in dilute hydrochloric acid (80 c.c.). The powdered arsinic acid (100 g.) and then ether (500 c.c.) were then added. Nitrogen was passed through the assembled apparatus in a slow stream throughout the experiment. Concentrated hydrochloric acid (600 c.c.) was added dropwise at the rate of 50 c.c./hr., with occasional shaking. The reaction was allowed to proceed at room temperature for 2 days, fresh ether being added when necessary.

The aqueous layer was extracted several times with ether, which was then forced by nitrogen pressure, first into a flask containing calcium chloride, and then in small portions into a Claisen flask, from which the ether was continuously distilled. The residue gave the arsine (IV) (18·2 g., 22%), b. p. 71—72°/15 mm., which was collected in a receiver suitable for the next operation. A non-volatile residue in the flask, probably dimethyldiphenyldiarsine, PhMeAs·AsMePh, melted at *ca.* 70°, and fumed when exposed to the air.

The low yield of the arsine (IV) is due primarily to evaporation in the current of hydrogen and nitrogen during reduction.

2-*Cyanoethylmethylphenylarsine* (V).—A mixture of the arsine (18·2 g.) and vinyl cyanide (12 g., *ca.* 2 mols.) was boiled under reflux in nitrogen for 4 hr. Distillation removed unchanged cyanide, and then gave the liquid *arsine* (V) (20·4 g., 85%), b. p. 117°/0·5 mm., 172—174°/14 mm. (Found : C, 54·2; H, 5·4; N, 6·3. $C_{10}H_{12}NAs$ requires C, 54·3; H, 5·5; N, 6·3%). The arsine slowly darkened in air. When mixed with an excess of methyl iodide it gave the *methiodide*, m. p. 164·5—165·5°, after repeated crystallisation from acetone (Found : C, 35·8; H, 3·8;

N, 3·9. $C_{11}H_{15}NIAs$ requires C, 36·4; H, 4·2; N, 3·9%). A mixture of the arsine and methyl toluene-*p*-sulphonate (1·1 mols.), when heated under nitrogen at 130° for 3 hr., gave a glass, which afforded crystals when its methanolic solution was cautiously diluted with ether. Recrystallisation in turn from ethanol, methanol–ether, and chloroform–light petroleum (b. p. 80—100°) ultimately gave the pure *metho-toluene*-p-*sulphonate*, m. p. 144—145° (Found: C, 52·7; H, 5·1. $C_{18}H_{22}O_3NSAs$ requires C, 53·1; H, 5·4%). This gave the yellow *metho-picrate*, m. p. 117—118° after crystallisation from water (Found: C, 44·0; H, 3·7; N, 12·3. $C_{17}H_{17}O_7N_4As$ requires C, 44·0; H, 3·7; N, 12·1%).

An acetone solution of the arsine, when diluted with " 10-vol." hydrogen peroxide, became warm. Removal of the solvent left a gum which could not be crystallised. A solution of the gum in warm dilute nitric acid, when evaporated to dryness in a vacuum, deposited the crystalline *hydroxynitrate*, m. p. 118—120° after crystallisation from ethanol (Found: C, 40·6; H, 4·2; N, 9·55. $C_{10}H_{13}O_4N_2As$ requires C, 40·0; H, 4·4; N, 9·3%).

As a brief example of the attempted cyclisation, the cyano-arsine (V) (1·3 g.) was added to a mixture of sodium chloride (1 g.), potassium chloride (1 g.), and aluminium chloride (5 g.) at 130°, with vigorous stirring for 1·5 min. The molten mass was poured on ice, basified with sodium hydroxide, warmed to 70° for 30 min., cooled, and extracted with benzene. Evaporation gave a non-ketonic residue, consisting almost wholly of the unchanged nitrile, characterised as its methiodide, m. p., alone and mixed, 163—165°. When the above melt was heated at 130° for 15 min., and at 180° for 20 min., the nitrile was still unchanged.

2-*Carboxyethylmethylphenylarsine* (VI).—A mixture of the nitrile (V) (10 g.) and a solution of potassium hydroxide (5 g.) in water (12·5 c.c.) and ethanol (12·5 c.c.) was boiled for 8 hr., evolution of ammonia then ceasing. The cold clear solution, when diluted with water (75 c.c.) and acidified (litmus) with concentrated hydrochloric acid, deposited the *arsine* as an oil (10·9 g., 99%), which when distilled in nitrogen had b. p. 138°/0·3 mm. and formed needles, m. p. 32° (Found: C, 49·7; H, 5·2. $C_{10}H_{13}O_2As$ requires C, 50·0; H, 5·5%).

The arsine in cold methyl iodide deposited the *methiodide*, which after crystallisation from acetone and then from methanol–ether melted at 110°, resolidified, and remelted at 151—153°; when rapidly heated it softened at *ca.* 110° and melted at 154° (Found: C, 34·8; H, 4·3. $C_{11}H_{16}O_2IAs$ requires C, 34·6; H, 4·2%).

An acetone solution of the arsine (VI), when treated with an excess of hydrogen peroxide (" 10-vol.") and evaporated, gave the *oxide*, m. p. 165° (from ethanol–ether) (Found: C, 46·8; H, 5·45. $C_{10}H_{13}O_3As$ requires C, 46·9; H, 5·1%).

The arsine gave an S-*benzylthiuronium salt*, m. p. 137° from ethanol–ether (Found: C, 52·8; H, 5·6. $C_{18}H_{22}O_4N_2SAs$ requires C, 53·1; H, 5·7%).

Attempts to cyclise this acid and its chloride under a variety of conditions failed. It is noteworthy that when a solution of the acid (1·2 g.) in concentrated sulphuric acid (4 c.c.) was heated at 100° for 1 hr. and cooled, working up gave a sulphonic acid, presumably 2-*carboxyethylmethyl*-m-*sulphophenylarsine*, m. p. 158—159° (decomp.), from methanol–ether (Found: C, 37·7; H, 4·5. $C_{10}H_{13}O_5SAs$ requires C, 37·5; H, 4·1%).

m-Nitrophenylarsonic acid (VIII), prepared by Doak's method,[7] was purified by dissolution in aqueous sodium carbonate, filtration, and acidification to Congo-red with concentrated hydrochloric acid. This gave a purer product than recrystallisation from water, which Doak recommends.

m-*Aminophenylarsonic Acid* (IX).—Fine-mesh cast-iron filings (200 g.) were stirred for 30 min. with a boiling solution of sodium chloride (50 g.) in water (1 l.) under reflux in a 3-necked flask. The arsonic acid (VIII) (100 g.) was then added in small portions during 3 hr., and the mixture boiled for a further 3—4 hr. A solution of sodium hydroxide (40 g.) in water (300 c.c.) was added to the mixture, which was filtered at the pump: the iron residue was extracted with boiling water (200 c.c.). The combined filtrates were concentrated to *ca.* 400 c.c., made just acid (Congo-red) with concentrated hydrochloric acid, and cooled in ice-water. The arsonic acid (IX), m. p. 210—215° (decomp.), crystallised, the mean yield being 75 g. (85%).

m-*Methoxyphenylarsonic Acid* (VII).—(*A*) To obtain the pure acid, the acid (IX) was first converted by Jacobs and Heidelberger's method [21] into *m*-hydroxyphenylarsonic acid (X), m. p. 160—170° (decomp.) when recrystallised from water. A solution of this acid (1·5 g.) in water (2·5 c.c.) containing sodium hydroxide (0·5 g.) was shaken with methyl sulphate until clear: sodium hydroxide (0·25 g.) in water (1 c.c.), and methyl sulphate (0·6 c.c.) were then

[21] Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1919, **41**, 1440.

added with further shaking. Acidification (Congo-red) with dilute hydrochloric acid precipitated the *methoxy-acid* (VII) (1·2 g., 75%), which was recrystallised from water (Found: C, 36·2; H, 4·0. $C_7H_9O_4As$ requires C, 36·2; H, 3·9%). The acid has an indefinite m. p. when heated from room temperature, but melts completely if immersed at 136°.

(*B*) To obtain the crude acid (VII) suitable for the next stage, a solution of the amino-acid (IX) (180 g.) in ice-water (1500 g.) containing concentrated sulphuric acid (89 c.c., 2·0 mols.) was stirred vigorously whilst an aqueous solution of sodium nitrite (60 g., 1·05 mols.) was added dropwise. The solution was diluted with water (2 l.) and warmed to 60° until nitrogen evolution ceased (*ca.* 2 hr.). Barium hydroxide octahydrate (530 g.) was added, and the hot solution vigorously stirred to precipitate barium sulphate. The filtered solution was treated with sodium hydroxide (100 g.), concentrated to *ca.* 750 c.c., cooled to 40°, and again stirred whilst methyl sulphate (120 c.c.) was added dropwise, the temperature being kept below 70°. The solution was again cooled to 40°, sodium hydroxide (50 g.) added, and then methyl sulphate (120 c.c.) as before. The process was again repeated with sodium hydroxide (50 g.) and the sulphate (120 c.c.). The filtered solution was cooled, acidified (Congo-red) with concentrated hydrochloric acid, seeded, vigorously stirred, and set aside overnight. The crude yellow acid (VII) slowly separated in mean yield of 164 g. (85%).

(*C*) The acid (VII) was also prepared in 22% yield by the application of the Bart reaction under normal conditions to *m*-anisidine.

m-*Methoxyphenylarsine* (XI).—This was prepared precisely as methylphenylarsine (IV), from mercuric chloride (10 g.) in dilute hydrochloric acid (100 c.c.), zinc dust (250 g.), the crude acid (VII) (100 g.), and concentrated hydrochloric acid (750 c.c.). The *arsine* (55 g., 70%) was isolated as a foul-smelling, rapidly oxidised liquid, b. p. 107—108°/16 mm., 60—61°/1 mm. (Found: C, 46·0; H, 4·9. C_7H_9OAs requires C, 45·7; H, 4·9%).

m-*Methoxyphenylmethylarsine* (XII).—Freshly and finely cut sodium (2·5 g., 1 atom-equiv.) was added to liquid ammonia (*ca.* 150 c.c.) in a 250 c.c. flask fitted with a dropping-funnel, mercury-sealed stirrer, and an air-condenser loosely plugged with cotton-wool. The deep blue solution was allowed to boil for 2—3 min to expel all air, and the flask was then cooled in acetone–solid carbon dioxide. The dropping-funnel was filled with nitrogen and a solution of *m*-methoxyphenylarsine (XI) (20·2 g.) in dry ether (60 c.c.), which was then added dropwise to the stirred liquid ammonia, the blue colour of which changed ultimately to yellow. A few very small pieces of sodium (0·03—0·05 atom-equiv.) were now added until the blue colour which was formed locally took several seconds to disappear. A solution of methyl iodide in ether was finally added dropwise until the yellow colour was just discharged.

The ammonia was allowed to evaporate, and the ethereal residue was forced by nitrogen in portions into a Claisen flask, from which ether was distilled; the residual arsine was finally distilled under reduced pressure of nitrogen. The arsine (XII) (18·4 g., 85%) had b. p. 117—119°/15 mm.; it contained only a trace of *m*-methoxyphenyldimethylarsine (see below). Satisfactory analytical results could not be obtained (Found: C, 46·6; H, 5·9. Calc. for $C_8H_{11}OAs$: C, 48·5; H, 5·6%), probably owing to atmospheric oxidation, although this was less rapid than that of methylphenylarsine (IV).

2-*Cyanoethyl*-m-*methoxyphenylmethylarsine* (XIII; R = CN).—A mixture of the arsine (XII) (20 g.) and vinyl cyanide (10·7 g., 2 mols.) was heated under nitrogen at 100° for 6 hr. After the removal of the excess of vinyl cyanide, the residue, distilled under nitrogen at 1 mm., gave the fractions: (i) b. p. 76—78°; (ii) b. p. 78—148°; (iii) b. p. 148—152°. The very small fraction (i) was *m*-methoxyphenyldimethylarsine, present in the arsine (XII) used. Fraction (iii) was the *cyano-arsine* (XIII; R = CN), in *ca.* 90% yield; after redistillation it was isolated as an odourless oil (Found: C, 52·9; H, 5·8; N, 5·8. $C_{11}H_{14}ONAs$ requires C, 52·5; H, 5·6; N, 5·6%). It gave a *methiodide*, prisms, m. p. 148°, from methanol–ether (Found: C, 36·6; H, 4·3; N, 3·7. $C_{12}H_{17}ONIAs$ requires C, 36·7; H, 4·4; N, 3·6%), and a *methopicrate*, bright yellow crystals, m. p. 117—118°, from methanol (Found: C, 44·0; H, 4·4; N, 11·2. $C_{18}H_{18}O_8N_4As$ requires C, 43·7; H, 3·9; N, 11·3%).

The combined fractions (i) from several preparations, when redistilled under nitrogen, gave the pure m-*methoxyphenyldimethylarsine*, b. p. 123—124°/15 mm., which oxidised only very slowly in the air (Found: C, 51·2; H, 6·25. $C_9H_{13}OAs$ requires C, 51·0; H, 6·2%). It reacted vigorously with methyl iodide, giving a *methiodide*, prisms, m. p. 248—250°, from methanol (Found: C, 34·0; H, 4·8. $C_{10}H_{16}OIAs$ requires C, 33·9; H, 4·6%).

2-*Carboxyethyl*-m-*methoxyphenylmethylarsine* (XIII; R = CO_2H).—The cyanoarsine (XIII;

R = CN) (43·5 g.) was added to a solution of potassium hydroxide (20 g.) in water (50 c.c.) and ethanol (50 c.c.), which was boiled under nitrogen for 12 hr. The cold solution was diluted with water (300 c.c.) and twice extracted with benzene, the extracts being rejected. The solution was acidified (litmus) with concentrated hydrochloric acid and again extracted with benzene. The extract was dried (Na_2SO_4) and the benzene removed by distillation in nitrogen. The carboxy-arsine (XIII; R = CO_2H) (45·3 g., 97%) remained as an almost colourless syrup; distillation gave a clear syrup, b. p. 166—172°/0·02 mm., 138—146°/0·003 mm., which did not solidify.

It readily gave a *methiodide*, crystals, m. p. 138°, from acetone and then methanol–ether (Found: C, 35·0; H, 4·4. $C_{12}H_{18}O_3IAs$ requires C, 35·0; H, 4·4%), and an S-*benzylthiuronium salt*, m. p. 138°, from ethanol (Found: C, 52·0; H, 6·1; N, 6·65. $C_{19}H_{25}O_3N_2SAs$ requires C, 52·3; H, 5·8; N, 6·4%).

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1-*methyl*-4-*oxoarsinoline* (XIV).—Phosphoric anhydride (40 g.) and " Hyflo Supercel " (20 g.) (included to prevent caking of the anhydride) were added to a solution of the carboxyarsine (XIII; R = CO_2H) (10 g.) in xylene (200 c.c.), which was boiled under reflux with vigorous stirring, in nitrogen for 2 hr. The xylene was separated by decantation, and the sticky residue extracted with boiling xylene (2 × 100 c.c.). The residue was then decomposed by the addition of ice, and the solution filtered to remove the Supercel, and extracted with benzene. The combined yellow xylene and benzene extracts were shaken with aqueous sodium carbonate, dried (Na_2SO_4), and evaporated under reduced pressure of nitrogen. The residual gum, when distilled in nitrogen, had b. p. 109—111°/0·02 mm., and the pale yellow distillate solidified on being scratched. In all subsequent preparations, the gum could be crystallised directly by dissolving in a minimum of ethanol and cooling the filtered solution in acetone–solid carbon dioxide, with scratching and seeding if required, the crystals being collected in a cooled filter. Repetition of this recrystallisation gave the pure *oxo-arsine* (XIV) (3·5 g., 38%), m. p. 52° (Found: C, 52·2; H, 5·2%; *M*, in boiling ethanol, 260. $C_{11}H_{13}O_3As$ requires C, 52·4; H, 5·2%; *M*, 252).

Alternatively, a solution of the carboxy-arsine (5 g.) in a mixture of phosphoric anhydride (25 g.) and syrupy phosphoric acid (25 c.c.) was heated under nitrogen at 100° for 3 hr. The hot red mixture was poured into cold water (100 c.c.), and the solution extracted with benzene. The benzene extract, treated as before, gave the residual gum, which on crystallisation afforded the oxo-arsine (XIV) (1·2 g., 26%).

The oxo-arsine readily gave a *methiodide*, prisms, m. p. 239°, from methanol (Found: C, 37·0; H, 4·4. $C_{12}H_{16}O_2IAs$ requires C, 36·6; H, 4·1%), and a *methopicrate*, yellow crystals, m. p. 226°, from water (Found: C, 43·7; H, 4·1; N, 8·6. $C_{18}H_{18}O_9N_3As$ requires C, 43·65; H, 3·7; N, 8·5%). When fused with methyl toluene-*p*-sulphonate (1·1 mol.) under nitrogen at 130° for 10 min., it gave the *methotoluene*-p-*sulphonate*, prisms, m. p. 180—205° (decomp.) from methanol (Found: C, 52·1; H, 5·6. $C_{19}H_{23}O_5SAs$ requires C, 52·1; H, 5·3%). The *semicarbazone* formed needles, m. p. 208°, from ethanol (Found: C, 46·55; H, 5·25; N, 13·7. $C_{12}H_{16}O_2N_3As$ requires C, 46·6; H, 5·2; N, 13·6%).

The *phenylhydrazone* was best prepared by heating a solution of the oxo-arsine (1 g.) and pure phenylhydrazine (0·45 g., 1·05 mol.) in ethanol (10 c.c.) and acetic acid (1 c.c.) under reflux in nitrogen for 8 hr. On cooling, the hydrazone separated as plates (92% yield), m. p. 121—122° after recrystallisation from ethanol (Found: C, 59·9; H, 5·7; N, 8·2. $C_{17}H_{19}ON_2As$ requires C, 59·7; H, 5·6; N, 8·2%). The 2 : 4-dinitrophenylhydrazone, when prepared in ethanol, separated as deep purple crystals, m. p. 183° after crystallisation from ethyl acetate or much ethanol, but a satisfactory analysis was not obtained (Found: C, 48·0; H, 4·5; N, 12·5. Calc. for $C_{17}H_{17}O_5N_4As$: C, 47·2; H, 4·0; N, 13·0%).

The oxo-arsine in acetone underwent vigorous oxidation when hydrogen peroxide was added, but only a dark tar was obtained.

3-(p-*Dimethylaminobenzylidene*)-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-1-*methyl*-4-*oxoarsinoline* (XX).—A solution of the oxo-arsine (0·50 g.) and *p*-dimethylaminobenzaldehyde (0·33 g., 1·1 mols.) in ethanol (10 c.c.) and 10% aqueous sodium hydroxide (0·5 c.c.) was boiled under reflux in nitrogen for 4 hr., and then concentrated to half-bulk and cooled. The orange solution deposited the *compound* (XX) as yellow needles (0·25 g.), m. p. 159° after crystallisation from ethanol: they were dried by heating at 60°/0·1 mm. for 6 hr. (Found: C, 61·8; H, 5·9; N, 3·6. $C_{20}H_{22}O_2NAs$ requires C, 62·7; H, 5·8; N, 3·7%).

The oxo-arsine (500 mg.) and then *p*-nitrosodimethylaniline (325 mg., 1·1 mol.) were added

XUM

in turn to a solution of sodium (50 mg., 1·1 atom-equiv.) in ethanol, and the brown mixture was shaken for 3 hr. The orange-brown crystals (400 mg.) which separated had m. p. 157° after crystallisation from ethanol: they were 3-(p-*dimethylaminophenylimino*)-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-1-*methyl*-4-*oxoarsinoline* (Found: C, 60·2; H, 5·9; N, 7·85. $C_{19}H_{21}O_2N_3As$ requires C, 59·4; H, 5·5; N, 7·3%), possibly slightly contaminated with azoxydimethylaniline (Calc. for $C_{16}H_{20}ON_4$: C, 70·1; H, 6·6; N, 18·2%), which *p*-nitrosodimethylaniline is known to give in the presence of potassium ethoxide even at 0°.[22] The same product was obtained in ethanol, more slowly and in smaller yield, when the sodium ethoxide was replaced by an equivalent of aqueous 10% sodium hydroxide.

The hydrolysis of this compound by acids, in the hope of obtaining the 3 : 4-dioxo-arsine, gave solely dark brown tars.

Di-(2-*cyanoethyl*)-m-*methoxyphenylarsine* (XV; R = CN).—The arsine (XI) (38·4 g.) and vinyl cyanide (33·5 g., 3 mols.) were heated under reflux in nitrogen at 100° for 6 hr. The excess of vinyl cyanide was removed by distillation, leaving a yellow viscous residue of the *dicyano-arsine* (XV; R = CN) (60·2 g., 100%), which was normally used without purification. A small quantity, distilled under nitrogen, afforded the cyano-arsine as a pale yellow odourless distillate, b. p. 206—212°/0·03 mm. (Found: N, 9·6. $C_{13}H_{15}ON_2As$ requires N, 9·7%): a slight residue of arsenic remained in the distilling-flask. The arsine reacted with methyl iodide to form a gum which gave an oily methopicrate.

Di-(2-*carboxyethyl*)-m-*methoxyphenylarsine* (XV; R = CO_2H).—This arsine was prepared by alkaline hydrolysis of the dicyano-arsine, precisely as the acid (XIII; R = CO_2H), and obtained as a colourless gum (95% yield), which slowly crystallised. It was too soluble in organic solvents for crystallisation: a sample reprecipitated from sodium hydroxide solution by hydrochloric acid had m. p. 54°, but was not pure (Found: C, 48·5; H, 5·05. Calc. for $C_{13}H_{17}O_5As$: C, 47·6; H, 5·2%). It readily gave a *methiodide*, m. p. 162° from methanol–ether (Found: C, 36·4; H, 4·2. $C_{14}H_{20}O_5IAs$ requires C, 35·8; H, 4·3%), which appeared to lose methyl iodide when dried; and a *bis*-S-*benzylthiuronium salt*, prisms, m. p. 134°, from methanol–ether (Found: C, 52·5; H, 5·3; N, 8·6. $C_{29}H_{37}O_5N_4S_2As$ requires C, 52·7; H, 5·65; N, 8·5%).

7-*Methoxy*-1 : 6-*dioxoarsulolidine* (XVI).—Phosphoric anhydride (20 g.) and "Hyflo Supercel" (10 g.) were added to a solution of the dicarboxy-arsine (XV; R = CO_2H) (10 g.) in dry toluene (200 c.c.), which was boiled under reflux with vigorous stirring for 15 min. The toluene was decanted from the sticky residue, which was extracted with boiling toluene (2 × 100 c.c.). The combined toluene extracts were shaken with aqueous sodium hydroxide, dried (Na_2SO_4), and evaporated under reduced pressure in nitrogen. The highly crystalline residual *arsulolidine* (XVI) formed rods, m. p. 150°, from ethanol or benzene (Found: C, 53·5; H, 4·8%; *M*, in freezing ethylene dibromide, 280. $C_{13}H_{13}O_3As$ requires C, 53·45; H, 4·5%; *M*, 292). The arsulolidine was recovered unchanged from the dibromide solution: the mean yield was 1·0 g., 11%. The dioxo-arsine is slightly volatile in boiling toluene, and the distillate was therefore used as solvent for the next cyclisation.

The sodium hydroxide extracts were acidified and extracted with benzene, but the extracts on evaporation gave only a trace of gummy residue.

The phosphoric anhydride residue, when treated as described on p. 3344, yielded a small quantity of the dioxo-arsine.

The dicarboxy-arsine (XV; R = CO_2H) (5 g.) was also treated with phosphoric anhydride and phosphoric acid for 1 hr. (see p. 3344). The yellow benzene extract, when shaken with aqueous sodium hydroxide, dried, and evaporated in nitrogen, gave a brown gum (0·85 g.), which on recrystallisation from benzene (seeding) gave the pure dioxo-arsine (XVI) (0·3 g., 7%). The alkaline extract was acidified and extracted with benzene, which on evaporation in nitrogen gave a brown ketonic gum (0·75 g.), apparently crude 1-(2-carboxyethyl)-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxoarsinoline, which did not crystallise. The only crystalline derivative isolated was the 2 : 4-dinitrophenylhydrazone, m. p. *ca.* 100° after crystallisation from ethanol–ethyl acetate, but this was still impure (Found: C, 47·6; H, 3·9; N, 12·0. Calc. for $C_{19}H_{19}O_7N_4As$: C, 46·5; H, 3·9; N, 11·4%).

A solution of the dioxo-arsine (XVI) (1 g.) and phenylhydrazine (0·82 g., 2·2 mols.) in ethanol (20 c.c.) and acetic acid (2 c.c.), when boiled under reflux in nitrogen for 6 hr., deposited the very pale cream crystalline *bisphenylhydrazone* (1·44 g., 89%), m. p. 169—171° after

[22] Hantzsch and Lehmann, *Ber.*, 1902, **35**, 897.

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crystallisation from ethanol–benzene (Found: C, 63·95; H, 5·5; N, 11·8. $C_{23}H_{25}ON_4As$ requires C, 63·6; H, 5·3; N, 11·9%).

The *bismethylphenylhydrazone*, similarly prepared, separated as pale cream needles (32%), m. p. 160° when recrystallised from ethanol (Found: C, 64·7; H, 5·4. $C_{27}H_{29}ON_4As$ requires C, 64·8; H, 5·8%. Low and inconsistent nitrogen values were always obtained).

The bisdiphenylhydrazone, similarly prepared, formed a brown gum.

When the dioxo-arsine in ethanol was warmed with a deficit of ethanolic 2 : 4-dinitrophenylhydrazine for 1—2 min., small deep purple crystals separated, and after crystallisation from ethanol afforded the *mono*-2 : 4-*dinitrophenylhydrazone ethanolate*, m. p. 125° (decomp.) (Found: C, 49·0; H, 4·3. $C_{19}H_{17}O_6N_4As,C_2H_6O$ requires C, 48·7; H, 4·5%). The use of an excess of the reagent, with boiling under reflux for 30 min., gave the very insoluble bright red crystalline *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 140° (decomp.) after washing with hot ethanol (Found: N, 17·3. $C_{25}H_{21}O_9N_8As$ requires N, 17·2%).

The dioxo-arsine in ethanolic solution, when heated for 15 min. with aqueous hydroxylamine hydrochloride (1·1 mol.) and sodium carbonate, gave the *mono-oxime*, prisms, m. p. 181°, from ethanol (Found: C, 51·3; H, 4·3; N, 4·4. $C_{13}H_{14}O_3NAs$ requires C, 50·9; H, 4·6; N, 4·6%).

The dioxo-arsine was recovered unchanged after its solution in methyl iodide had been boiled in nitrogen for 6 hr. A mixture of the arsine and methyl toluene-*p*-sulphonate (1·1 mol.), when fused under nitrogen at 130° for 15 min., cooled, and extracted with ether, gave a red-brown gum.

No satisfactory product could be isolated on interaction of the dioxo-arsine with *p*-dimethylaminobenzaldehyde or with *p*-nitrosodimethylaniline under various conditions.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 13th*, 1957.]

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667. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part VIII.* Derivatives of* 1 : 2 : 3 : 4-*Tetrahydro*-4-*oxoarsinoline and of* 1 : 6-*Dioxoarsulolidine.*

By FREDERICK G. MANN and A. J. WILKINSON.

1 : 2 : 3 : 4-Tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline has been (*a*) converted *via* its phenylhydrazone into the indolo(3′ : 2′-3 : 4)arsinoline, and (*b*) converted by the Friedlander and the Pfitzinger reaction into the quinolino(3′ : 2′-3 : 4)arsinoline and its 4′-carboxylic acid respectively. 7-Methoxy-1 : 6-dioxoarsulolidine has been similarly converted into the indolo(2′ : 3′-1 : 2)arsuloline and the quinolino(2′ : 3′-1 : 2)arsuloline derivatives.

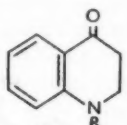
The properties of these compounds, particularly in comparison with those of their nitrogen analogues, are discussed.

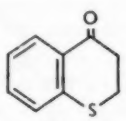
EARLIER Parts of this series contain a discussion of the structure of the indolo- and quinolino-derivatives of, in particular, various substituted 1 : 2 : 3 : 4-tetrahydro-4-oxoquinolines (I), where the substituent R has been a single group, or a portion of another ring. The main points arising in the structures of these derivatives may be briefly summarised: Indolisation of the phenylhydrazone of the oxo-amine (I) [1,2,3] gives a coloured ψ-indole, which readily adds acids to give colourless salts, in which the proton and the positive charge have been accepted by the indolo- and the quinolino-nitrogen atom respectively.

* Part VII, *J.*, 1955, 393.

[1] Mann, *J.*, 1949, 2816.
[2] Mann and Smith, *J.*, 1951, 1898.
[3] Braunholtz and Mann, *J.*, 1955, 381.

The application of the Pfitzinger reaction to the oxo-amine (I) has given a deep red 4′-carboxyquinolino-derivative, the colour of which is due to the formation of a zwitterion, which has a number of canonical forms, one having the positive charge on the original quinolino-nitrogen atom. This zwitterion, on being heated, undergoes decarboxylation to a cream-yellow amine, which in hot acids undergoes the " allylic " transformation to to give an isomer: both isomers are oxidised readily in solution to give the cyclic acid amide in which the 2-methylene group in the quinoline (I) has become a $>CO$ group.


(I)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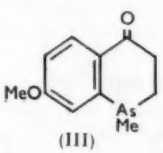
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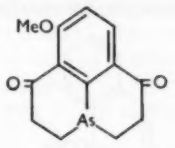

(IV)

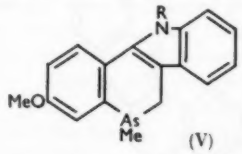
To determine whether the above properties, and particularly the high degree of resonance shown by the zwitterion, were determined specifically by the nitrogen group in (I), Kiang and Mann [4] repeated these reactions with 4-oxothiochroman (II), in which the sulphur atom in the corresponding derivatives could theoretically accept the positive charge previously carried by the nitrogen atom in (I). It was found that the compound (II) gave a normal indolo-derivative, and in the Pfitzinger reaction gave a 4′-carboxyquinolino-derivative which again formed a zwitterion but on decarboxylation gave an amine which did not undergo atmospheric oxidation at the 2-methylene group.

The synthesis of 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline [5] (III) has now, however, provided a compound much more strictly analogous to the corresponding oxo-quinoline (I; R = Me) [3] than was the 4-oxothiochroman (II), and we have applied the above reactions both to this oxo-arsine (III) and to 7-methoxy-1 : 6-dioxoarsulolidine [5] (IV), which is the arsenic analogue of 1 : 6-dioxojulolidine [6] previously investigated.

Indolisation of the phenylhydrazone of the oxo-arsine (III) to give cream-coloured 1 : 2-dihydro-7-methoxy-1-methylindolo(3′ : 2′-3 : 4)arsinoline (V; R = H) required heating with zinc chloride and acetic acid, conditions much more vigorous than those necessary [3] with the phenylhydrazone of the quinoline (I; R = Me). On the other hand, indolisation of the methylphenylhydrazone and the diphenylhydrazone of the arsine (III) to give the colourless 1 : 1′-dimethyl and 1-methyl-1′-phenyl derivatives (V; R = Me and Ph respectively) proceeded very readily in hot ethanol–acetic acid.

The fact that the product from the phenylhydrazone is the true indole (V; R = H) and not the ψ-indole (VI) is clearly shown by its lack of colour, its non-basic character, and by its infrared spectrum, which shows a marked band at 2·96 μ due to the $>NH$ group.

It is, therefore, noteworthy that, although all the phenylhydrazones of the 4-oxo-quinolines of type (I) have, with one exception,[6] given ψ-indoloquinolines, this process does not occur in the corresponding indoloarsinolines (V). One potent factor in this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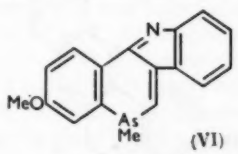
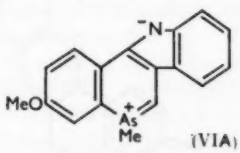

(VI)


(VIA)

difference is that the yellow colour, and the avidity for union with acids and alkyl halides, shown by the ψ-indoloquinolines indicate a considerable degree of charge separation between the two nitrogen atoms, of which the counterpart in the ψ-indoloarsindole (VI)

[4] Kiang and Mann, *J.*, 1951, 1909.
[5] Mann and Wilkinson, preceding paper.
[6] Braunholtz and Mann, *J.*, 1955, 393.

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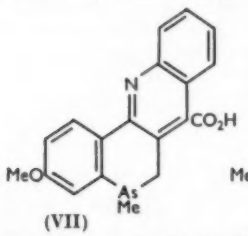
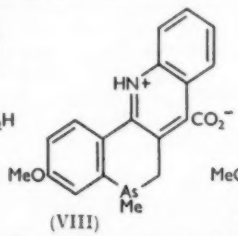
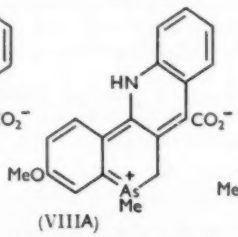
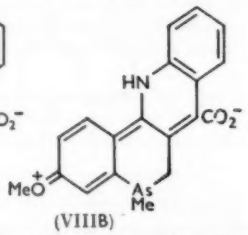
would be (VIA): salt formation with acids and alkyl halides then involves solely the addition of a proton or an alkyl group to the negative nitrogen in (VIA). But the disposition of the arsenic valencies in the ring system in (VIA)—and all the properties such a disposition would imply—are very rarely found (see preceding paper [5]) and presumably either are normally physically impossible or entail great instability, and hence the stable indoloarsinoline (V; R = H) is formed.

In the application of the Pfitzinger reaction, the oxo-arsine (III) and isatin in aqueous-ethanolic potassium hydroxide were boiled for 48 hours. Addition of acetic acid deposited


(VII)


(VIII)

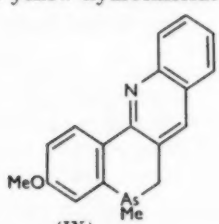

(VIIIA)

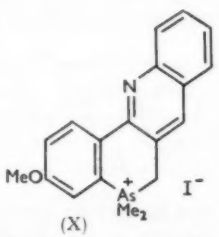

(VIIIB)

the yellow 1 : 2-dihydro-7-methoxyquinolino(3′ : 2′-3 : 4)arsinoline-4′-carboxylic acid (VII), which was insoluble in the usual solvents and could not be satisfactorily purified by recrystallisation or reprecipitation. In an attempted decarboxylation, the acid was heated in a high vacuum, a process, however, which yielded the pure unchanged crystalline acid. This distilled acid proved surprisingly to be the zwitterion (VIII), for its infrared spectrum showed no band in the 3 μ region, where a free $>$NH group would have become apparent, but showed a broad ill-defined band at 4·9 μ, attributed to the $\dot{}NH^+$ group, and two bands at 6·15 and 6·24 μ characteristic of the CO_2^- ion in amino-acids having the zwitterion structure.[3, 6] Such volatilisation without decomposition of amino-acids having this structure is rare: it is possible that the zwitterion (VIII) reverts to the covalent state (VII) in the vapour phase, and returns to the polar state (VIII) on solidification.

The fine structure of this acid (VIII) is of considerable interest. Apart from the methoxyl group, it is strictly analogous to the deep red zwitterion formed by 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline-4′-carboxylic acid,[3] the intense colour of which is undoubtedly partly caused by a marked contribution by the canonical form having a positive charge on the methylated amine group, but in the quinolinoarsinoline (VIII) the corresponding form (VIIIA) almost certainly does not exist. On the other hand, the canonical form (VIIIB) has necessarily no counterpart in our nitrogen analogues which do not contain a methoxyl group.

The acid (VIII) dissolves in aqueous sodium and potassium hydroxide to give colourless solutions, the resonance shown by the zwitterion being now absent. It also gives an unstable yellow hydrochloride.


(IX)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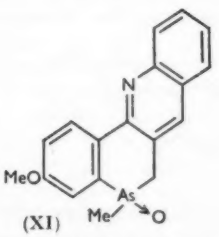
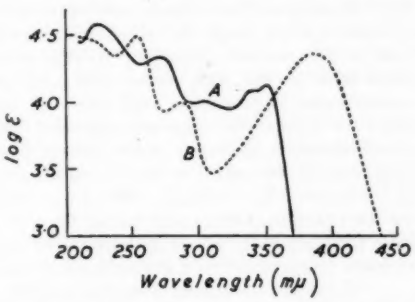

(XI)

Since the acid (VIII), unlike its nitrogen analogue, does not undergo decarboxylation when heated in a vacuum, the corresponding base, 1 : 2-dihydro-7-methoxy-1-methylquinolino(3′ : 2′-3 : 4)arsinoline (IX), was prepared by direct condensation of the oxo-arsine (III) and *o*-aminobenzaldehyde in an alkaline medium at room temperature. This

colourless base readily forms, at room temperature, an almost colourless methiodide, which must have the structure (X), for the nitrogen atom in these fused-ring systems usually requires vigorous conditions for quaternisation. The base (IX) formed a yellow hydrochloride, and the methiodide (X) formed a yellow methiodide hydriodide. These facts indicate strongly that, in the acid (VIII) and in derivatives of the base (IX), the yellow colour is directly associated with protonation of the nitrogen atom and, although the evidence is inconclusive, the colour may be due to resonance contributed by canonical forms of type (VIII) and (VIIIB). The Figure shows the ultraviolet absorption curves of the base (IX) in (*A*) ethanol, and (*B*) ethanol–hydrochloric acid. The curve (*B*) is similar in type to (*A*) with the main features now more prominent, and in particular with a general shift to longer wavelengths, the broad band at 385 mμ being responsible for the yellow colour. For comparable curves for the nitrogen analogue, 1 : 2-dihydro-1-methylquinoline(3′ : 2′-3 : 4)quinoline, see Braunholtz and Mann.[3]

The base (IX), unlike its nitrogen analogue, gave no indication of allylic isomerism when treated with hot acids. This is in accordance with the mechanism of this process



1 : 2-Dihydro-7-methoxy-1-methylquinolino(3′ : 2′-3 : 4)arsinoline (IX) *in* (*A*) *ethanol,* (*B*) *in ethanol diluted with an equal volume of* N/10-*hydrochloric acid.*

suggested by Braunholtz and Mann,[3] the first stage of which is the migration of a proton from the 1′-nitrogen atom to a basic hetero-atom in position 1 : in view of the neutral character of tertiary arsines,[7] this stage is clearly not possible in salts of the base (IX). Further, the base did not undergo atmospheric oxidation in organic solvents, although when treated with potassium permanganate it gave the expected arsine oxide (XI).

The bisphenylhydrazone of 7-methoxy-1 : 6-dioxoarsulolidine (IV), when heated in acetic acid containing zinc chloride, gave 7-methoxy-6-oxoindolo(2′ : 3′-1 : 2)arsuloline (XII), one of the hydrazone groups having undergone indolisation, and the other hydrolysis with regeneration of the oxo-grouping. This result is not unexpected, for Ittyerah and Mann [8] have shown that a 7-methyl group in 1 : 6-dioxojulolidine exerts a powerful steric influence on the neighbouring 6-oxo-group, an influence which, whilst allowing phenylhydrazone formation, suppresses several other reactions such as condensation with malononitrile. Further, the bisphenylhydrazone of *cyclo*hexane-1 : 2-dione under various conditions also undergoes indolisation of one hydrazone residue and hydrolysis of the other residue, with the formation of 1 : 2 : 3 : 4-tetrahydro-1-oxocarbazole.[9]

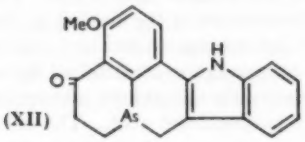
The structure of the compound (XII) is confirmed by its infrared spectrum which shows a band at 3·03 μ, attributed to the >NH group, and one at 6·02 μ, attributed to the >CO group. In this compound, therefore, no question of ψ-indole formation arises, undoubtedly for the same reasons as those previously discussed regarding the compound (V; R = H).

Application of the Pfitzinger reaction to the dioxoarsine (IV) gave only tarry products. The milder conditions of the Friedlander reaction, using *o*-aminobenzaldehyde, gave

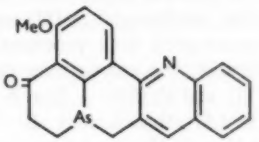
[7] Davies and Addis, *J.*, 1937, 1622.
[8] Ittyerah and Mann, *J.*, 1956, 3179.
[9] Plancher, Cecchetti, and Ghigi, *Gazzetta*, 1929, **59**, 346; Bloink and Pausacker, *J.*, 1950, 1328.

XUM

7-methoxy-6-oxoquinolino(2′ : 3′-1 : 2)arsuloline (XIII), which after distillation formed a glass which could not be crystallised but gave a crystalline picrate. It is noteworthy that, in this reaction also, in spite of the use of an excess of the aldehyde, only one of the



(XII)



(XIII)

oxomethylene groups has undergone condensation, the other being again obstructed by the methoxyl group. Lack of material precluded further investigation of the properties of the compound (XIII).

Experimental

o-Aminobenzaldehyde.—The reported instability of this compound has been exaggerated. The following method, which is essentially a simplification of the recorded preparation,[10] gave a product which could be stored unchanged in a refrigerator for several weeks. A 3-necked flask of 1 l. capacity, fitted for stirring and rapid distillation of its contents, was placed in a water-bath at 90°, and water (175 c.c.), powdered ferrous sulphate heptahydrate (105 g.), concentrated hydrochloric acid (0·5 c.c.) and *o*-nitrobenzaldehyde (6 g.) were added in that order. Concentrated aqueous ammonia (25 c.c.) was added in one portion to the vigorously stirred mixture, and then three further portions, each of 10 c.c., at 2 min. intervals. After 8 min. in all, the mixture was steam-distilled as rapidly as possible, the receiver being cooled in ice-water. The distillate (500 c.c.), collected in *ca.* 20 min., was treated with powdered sodium chloride (140 g.) and stirred for 1 hr. at 5°, and the almost colourless *o*-aminobenzaldehyde (2·65 g., 55%) which had separated was collected, washed with ice-cold water, and dried at room temperature and atmospheric pressure.

1 : 2-*Dihydro*-7-*methoxy*-1-*methylindolo*(3′ : 2′-3 : 4)*arsinoline* (V; R = H).—A solution of the phenylhydrazone (0·5 g.) of the oxo-arsine (III) in glacial acetic acid (5 c.c.) containing pulverised zinc chloride (0·5 g.) was boiled under reflux in nitrogen for 15 min., and water was then added dropwise to the hot solution until a permanent turbidity was produced. The solution, when allowed to cool spontaneously, gave a deposit, partly tar and partly crystalline, which when recrystallised from aqueous ethanol gave the very pale cream-coloured *indoloarsinoline* (V; R = H), m. p. 137—139° (Found: C, 62·4; H, 5·3; N, 4·6. $C_{17}H_{16}ONAs$ requires C, 62·8; H, 5·0; N, 4·3%).

Only tarry products were isolated by boiling solutions of the phenylhydrazone in ethanolic hydrogen chloride, pure acetic acid, or acetic acid either saturated with hydrogen chloride or containing 10% of concentrated hydrochloric acid. The hydrazone was recovered unchanged after being heated with dilute sulphuric acid at 100° for 30 min.

1 : 2-*Dihydro*-7-*methoxy*-1 : 1′-*dimethylindolo*(3′ : 2′-3 : 4)*arsinoline* (V; R = Me).—A solution of the oxo-arsine (0·5 g.) and methylphenylhydrazine (0·26 g., 1·1 mol.) in ethanol (5 c.c.) containing acetic acid (0·5 c.c.) was boiled under nitrogen for 8 hr. The pale yellow precipitate (0·32 g., 48%) which separated on cooling, when recrystallised from ethanol, afforded the colourless *indoloarsinoline*, m. p. 115° (Found: C, 63·7; H, 5·05; N, 4·35. $C_{18}H_{18}ONAs$ requires C, 63·7; H, 5·3; N, 4·1%).

The 1-*methyl*-1′-*phenylindoloarsinoline* (V; R = Ph) was similarly prepared in 30% yield by using *as.*-diphenylhydrazine, and formed colourless plates, m. p. 157°, from ethanol (Found: C, 69·0; H, 5·2; N, 3·6. $C_{23}H_{20}ONAs$ requires C, 68·8; H, 5·0; N, 3·5%).

1 : 2-*Dihydro*-7-*methoxy*-1-*methylquinolino*(3′ : 2′-3 : 4)*arsinoline*-4′-*carboxylic Acid* (VII).—A solution of the oxo-arsine (III) (0·50 g.), isatin (0·30 g., 1·05 mol.) and potassium hydroxide (0·40 g.) in ethanol (4 c.c.) and water (1 c.c.) was boiled under reflux in nitrogen for 48 hr. The cold solution was poured into an excess of 10% aqueous acetic acid, giving a yellow precipitate (0·40 g., 53%) which was collected, washed with water, and dried. When it was heated in a glass tube at 250°/0·0005 mm., a yellow glass condensed on the cold portion of the tube. This glass crystallised when subsequently rubbed with boiling ethanol, in which it was insoluble, and

[10] Smith and Opie, *Org. Synth.*, 1948, **28**, 11.

afforded the pure yellow *acid* (VII), m. p. 220—250° (decomp.) after drying at 60°/0·1 mm. for 6 hr. (Found : C, 59·7; H, 4·5; N, 3·6. $C_{19}H_{16}O_3NAs$ requires C, 59·9; H, 4·2; N, 3·7%).

When the period of boiling was reduced to 24 hr., the yield was substantially reduced.

The acid appeared to be completely stable in air. When added to warm concentrated hydrochloric acid, it dissolved to give a yellow solution, from which the yellow hydrochloride rapidly separated. This salt was too unstable to be purified, and showed a m. p. identical with that of the acid, undoubtedly because of complete dissociation during heating.

When a mixture of equal weights of the acid and freshly powdered barium hydroxide (or soda-lime) was heated at 250°/0·001 mm., only a trace of a yellow glass condensed in the tube, and no evidence of decarboxylation could be obtained.

1 : 2-*Dihydro*-7-*methoxy*-1-*methylquinolino*(3′ : 2′-3 : 4)*arsinoline* (IX).—A solution of the oxo-arsine (III) (0·25 g.) and *o*-aminobenzaldehyde (0·13 g., 1·1 mols.) in ethanol (10 c.c.) was treated with 10% aqueous sodium hydroxide (0·5 c.c.) and set aside at room temperature for 3 days. It was then saturated with hydrogen chloride and taken to dryness on a steam-bath. The residue was dissolved in hot water (10 c.c.) and an excess of concentrated aqueous ammonia added, giving a gummy precipitate. In initial experiments, this precipitate, when collected, washed with water and dried, was heated at 180°/0·002 mm., giving a yellow distillate which on cooling formed a glass. Recrystallisation from warm ethanol (2—3 c.c.) yielded the colourless *arsinoline* (IX) (0·13 g., 39%), m. p. 136° (Found : C, 64·0; H, 4·8; N, 4·2. $C_{18}H_{16}ONAs$ requires C, 64·1; H, 4·8; N, 4·2%). In later preparations, when the crystalline product was available, the precipitate was recrystallised directly from ethanol, the solution on cooling being seeded and scratched to initiate the crystallisation.

A solution of the arsinoline (IX) (50 mg.) in ethanol (2 c.c.), when saturated with hydrogen chloride and then diluted with ether, deposited the yellow *hydrochloride*, which was purified by reprecipitation from ethanolic solution with ether, giving fine yellow crystals, m. p. 206° (decomp.), of the hydrated salt (Found : C, 54·4; H, 5·0; N, 3·45. $C_{18}H_{16}ONAs,HCl,1{\cdot}25H_2O$ requires C, 54·6; H, 5·0; N, 3·5%).

The yellow very insoluble *picrate*, m. p. 192°, was prepared in ethanol, and washed with hot ethanol (Found : C, 50·3; H, 3·1; N, 10·7. $C_{18}H_{16}ONAs,C_6H_3O_7N_3$ requires C, 50·9; H, 3·4; N, 9·9%).

A solution of the arsinoline (IX) in cold methyl iodide, when set aside overnight, deposited the almost colourless *methiodide* (X), m. p. 225° (decomp.) after washing with methyl iodide and ether (Found : C, 47·95; H, 3·9; N, 3·1. $C_{19}H_{19}ONIAs$ requires C, 47·6; H, 4·0; N, 2·9%) : it could not be satisfactorily recrystallised.

Pure hydriodic acid (of constant b. p.) was added dropwise in slight excess to a cold methanolic solution of the methiodide (X), which immediately developed a deep yellow colour. The solution, when filtered into much ether, deposited the yellow microcrystalline *methiodide hydriodide hydrate*, which was collected, washed with ether, and dried in a vacuum : it had an indefinite m. p., becoming completely molten by 225° (Found : C, 34·5; H, 3·8; N, 2·1. $C_{19}H_{19}ONIAs,HI,3H_2O$ requires C, 34·5; H, 4·0; N, 2·1%). Dehydration of this salt was not attempted, in case dissociation of the hydriodide also occurred.

A solution of the arsinoline (IX) (50 mg.) in benzene (2 c.c.) was exposed to the air for 3 days, evaporation losses being made good from time to time. The solution was then evaporated to dryness, but the brown semicrystalline residue on recrystallisation from ethanol afforded only the unchanged arsinoline (27 mg.). This stability to oxidation is in marked contrast to the ready oxidation in these conditions which quinolino(2′ : 3′-1 : 2)juloline and its isomer,[2] and also 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline (I; R = Me) and its isomer,[3] undergo.

A saturated solution of potassium permanganate in acetone was added dropwise to a solution of the arsinoline (IX) (0·15 g.) in acetone (15 c.c.) until the latter retained a faint purple colour. The solution was filtered from manganese dioxide, which was extracted with boiling acetone (20 c.c.). The combined acetone extracts when evaporated gave a pale brown residue, a solution of which in hot ethanol was filtered and again evaporated. The colourless needles of the *arsinoline oxide* (XI) thus obtained had m. p. 232° (decomp.) after recrystallisation from ethanol and drying in a vacuum (Found : C, 57·9; H, 5·3; N, 4·1. $C_{18}H_{16}O_2NAs,H_2O$ requires C, 58·2; H, 4·9; N, 3·8%). The infrared absorption showed (*a*) no carbonyl absorption in the 6 μ region, hence the oxidation has not produced the ·AsMe·CO· derivative, comparable to the nitrogen analogue, (*b*) broad absorption in the 2·88—2·96 μ region, indicating the presence of

water, and the compound is, therefore, not the :As(OH)$_2$ derivative isomeric with the hydrated oxide, for, in addition, the As(OH) group gives broad absorption above 3·3 μ.

The oxide in ethanol gave a *picrate*, yellow crystals, m. p. 192° (decomp.) after crystallisation from much ethanol (Found: C, 49·1; H, 3·3; N, 9·4. $C_{18}H_{16}O_2NAs,C_6H_3O_7N_3$ requires C, 49·5; H, 3·3; N, 9·6%). It is uncertain whether this picrate formation has occurred at the arsine oxide group or the nitrogen atom, but the former is the more likely.

7-*Methoxy*-6-*oxoindolo*(2′ : 3′-1 : 2)*arsuloline* (XII).—A solution of the bisphenylhydrazone (0·25 g.) of 7-methoxy-1 : 6-dioxoarsulolidine (IV) in glacial acetic acid (2·5 c.c.) containing zinc chloride (0·25 g.) was boiled under reflux in nitrogen for 3 hr., and water then added to the hot stirred solution until a permanent turbidity was obtained. The solution on cooling gave a gummy deposit, which on recrystallisation from aqueous ethanol afforded the almost colourless *indoloarsuloline* (XII), m. p. 232° (Found: C, 62·5; H, 4·9; N, 4·0. $C_{19}H_{16}O_2NAs$ requires C, 62·9; H, 4·4; N, 3·8%).

7-*Methoxy*-6-*oxoquinolino*(2′ : 3′-1 : 2)*arsuloline* (XIII).—A solution of the dioxo-arsine (IV) (0·20 g.) and *o*-aminobenzaldehyde (0·18 g., 2·2 mols.) in ethanol (20 c.c.) and 10% aqueous sodium hydroxide (0·7 c.c.) was set aside for 5 days, and then saturated with hydrogen chloride and evaporated to dryness. The residue, when stirred with hot dilute aqueous ammonia, gave an insoluble gum, which was collected, and dried. When heated at 200°/0·003 mm., it gave an orange distillate of the arsuloline (XIII), which on cooling formed a glass. This glass could not be induced to crystallise, and it was therefore treated with picric acid, both in ethanolic solution. The precipitated crystalline *picrate* of the arsuloline (XIII), when recrystallised from ethanol, formed the monoethanolate, yellow plates, m. p. 164—166° (Found: C, 51·35; H, 3·75; N, 8·7. $C_{20}H_{16}O_2NAs\,C_6H_3O_7N_3,C_2H_6O$ requires C, 51·55; H, 3·9; N, 8·6%).

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University Chemical Laboratory, Cambridge. [*Received, February 13th*, 1957.]

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668. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part IX.* Derivatives of* 1 : 3 : 4 : 5-*Tetrahydro*-5-*oxobenz*[cd]*indole.*

By Frederick G. Mann and A. J. Tetlow.

1 : 3 : 4 : 5-Tetrahydro-6-methoxy-1 : 2-dimethyl-5-oxobenz[*cd*]indole (V; R = OMe) has been prepared by direct cyclisation of 3-2′-carboxyethyl-1 : 2-dimethyl-5-methoxyindole, followed by remethylation of the intermediate 6-hydroxy-derivative.

The phenyl- and the *as.*-methylphenyl-hydrazone of this 6-methoxy-5-oxobenz[*cd*]indole undergo indolisation, but the infrared evidence indicates that the products, which can be isolated only as salts, are indoline isomers of the expected indolo-derivatives.

By the Pfitzinger reaction the 6-methoxy-5-oxobenz[*cd*]indole gives 4 : 6-dihydro-1-methoxy-4 : 5-dimethylindolo[3,4-*bc*]acridine-7-carboxylic acid, which forms a coloured zwitterion, like previous compounds of this class. When heated with hydrochloric acid, it undergoes allylic transformation to the 4 : 7-dihydro-isomer.

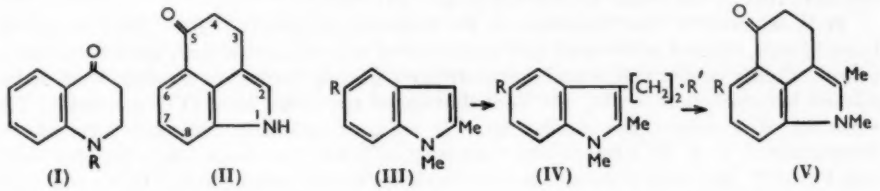
Decarboxylation of these two acids gives the corresponding isomeric 4 : 6-dihydro- and 4 : 7-dihydro-indolo-acridines. These differ from the isomeric pairs of such bases previously described, in that they are not interconvertible, and they give isomeric, instead of identical, oxidation products.

In previous papers in this series, the outstanding properties of the indolo-, quinolino-, and 4′-carboxyquinolino-derivatives obtained from various cyclic oxo-amines, such as

* Part VIII, preceding paper.

1 : 2 : 3 : 4-tetrahydro-4-oxo-1-phenyl(or methyl)quinoline (I; R = Ph or Me) [1,2] have been described and discussed. For a summary of these results see the preceding paper.[3]

In development of this work, we have investigated the preparation of suitable derivatives of 1 : 3 : 4 : 5-tetrahydro-5-oxobenz[*cd*]indole (II), a cyclic amino-ketone differing fundamentally in structure from all those previously studied in this series in that now the



amino- and the ketonic group are not in the same ring. The indole (II) has been prepared by Uhle,[4] and by Grob and Voltz,[5] in each case by a long route. To obtain a shorter synthesis, we initially (with the assistance of Dr. C. Y. Almond) converted 1 : 2-dimethylindole (III; R = H) by the action of vinyl cyanide into 3-2′-cyanoethyl-1 : 2-dimethylindole (IV; R = H; R′ = ·CN), the structure of which was placed beyond doubt by the presence of the two methyl groups in the indole (III). All attempts, under various conditions, to induce the required cyclisation of this cyano-compound failed, and the 2′-carboxyethyl derivative (IV; R = H; R′ = CO_2H) gave only an insignificant yield of ketonic product. A similar failure to induce cyclisation of 3-1′ : 2′-dicarboxyethyl-2-methylindole was later recorded by Plieninger.[6]

In order, therefore, to activate the indole in the 4-position, we have converted 5-methoxy-1 : 2-dimethylindole (III; R = OMe) into the 3-2′-cyanoethyl derivative (IV; R = OMe, R′ = CN). Hydrolysis of this derivative gave 3-2′-carboxyethyl-5-methoxy-1 : 2-dimethylindole (IV; R = OMe, R′ = CO_2H); this acid was also obtained by the action of β-propiolactone [7] on the indole (III; R = OMe), but the former method was preferable for reasonably large-scale work.

All attempts to cyclise the 2′-cyanoethyl derivative failed, but the 2′-carboxyethyl derivative, when heated with a mixture of sulphuric and phosphoric acid,[8] underwent cyclisation and demethylation, giving 1 : 3 : 4 : 5-tetrahydro-6-hydroxy-1 : 2-dimethyl-5-oxobenz[*cd*]indole (V; R = OH);* the yield was 32% after allowance for the 3-2′-carboxyethyl-5-hydroxy-1 : 2-dimethylindole (IV; R = OH, R′ = CO_2H) which was recovered and could be similarly cyclised directly to (V; R = OH). This is the first recorded example of this cyclisation in a true indole, although Woodward and his co-workers [9] subsequently carried out a similar cyclisation of a 3-2′-carboxyethylindoline.

Although the 6-hydroxybenz[*cd*]indole (V; R = OH) gave acetoxy- and toluene-*p*-sulphonyloxy-derivatives, and also a phenylhydrazone, without difficulty, it showed marked hydrogen-bonding between the hydroxyl and the carbonyl group, and methylation of the hydroxy-group was ultimately achieved only by treatment with 30% aqueous sodium hydroxide and a large excess (*ca.* 10 mols.) of methyl sulphate in acetone. Infrared spectra clearly indicate this hydrogen-bonding: the spectrum of the 6-hydroxy-compound

* In a preliminary note (Mann and Tetlow, *Chem. and Ind.*, 1953, 823) this indole was named the 6-methoxy-derivative (V; R = OMe) in error.

[1] Mann, *J.*, 1949, 2816.
[2] Braunholtz and Mann, *J.*, 1955, 381.
[3] Mann and Wilkinson, preceding paper.
[4] Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761.
[5] Grob and Voltz, *Helv. Chim. Acta*, 1950, **33**, 1796.
[6] Plieninger, *Chem. Ber.*, 1953, **86**, 404.
[7] Harley-Mason, *Chem. and Ind.*, 1951, 886; *J.*, 1952, 2433.
[8] Cf. Horning, Koo, and Walker, *J. Amer. Chem. Soc.*, 1951, **73**, 5827.
[9] Kornfeld, Fornefeld, Kline, Mann, Jones, and Woodward, *ibid*, 1954, **76**, 5256.

shows only an extremely weak band at 3·18 μ due to a hydroxyl group but a strong band at 6·08 μ due to the carbonyl group, whereas that of the 6-methoxy-compound shows a strong band at 6·00 μ.

The 6-hydroxy- and the 6-methoxy-benz[*cd*]indole (V; R = OH and OMe) form yellow and very pale yellow crystals respectively, but their ultraviolet spectra both closely resemble that of the unsubstituted compound (II) (Fig. 1).

It is noteworthy that solutions of the 6-methoxyindole (V; R = OMe) in carbon tetrachloride, ethanol, acetic acid, and concentrated hydrochloric acid are almost colourless, yellow, slightly deeper yellow and orange-red respectively, indicating strongly that, as the solvent becomes more acidic, the contribution of the polar form (VI) increases. The existence of a polar form similar to (VI) as a contributing canonical form of the unsubstituted 1 : 3 : 4 : 5-tetrahydro-5-oxobenz[*cd*]indole has been suggested by Grob and Payot.[10] We have obtained decisive evidence for the polar form (VI), for our compound (V; R = OMe) is markedly basic: its cold, almost colourless solution in benzene,

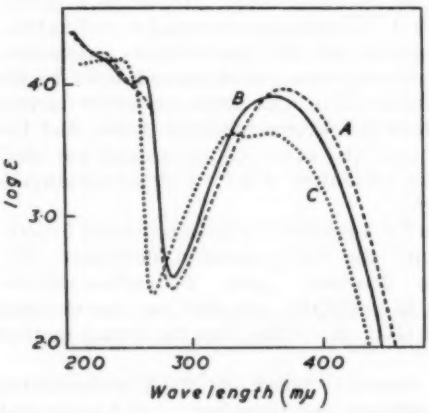
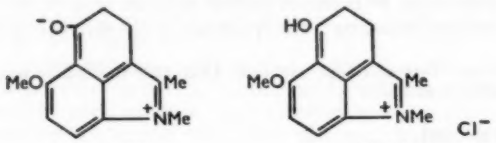


FIG. 1. *A*, 1 : 3 : 4 : 5-*Tetrahydro-6-hydroxy-1 : 2-dimethyl-5-oxobenz*[cd]*indole* (V; R = OH). *B*, 1 : 3 : 4 : 5-*Tetrahydro-6-methoxy-1 : 2-dimethyl-5-oxobenz*[cd]*indole* (V; R = OMe). *C*, 1 : 3 : 4 : 5-*Tetrahydro-5-oxobenz*[cd]*indole* (taken from ref. 5). All in ethanol.

when treated with dry hydrogen chloride, deposits deep garnet-red crystals of the unstable hydrochloride (VIA). The structure of this salt, and hence its formation by the protonation of the negative oxygen atom in (VI), are confirmed by the infrared spectrum, which gives strong evidence for the presence of an OH group, very feeble evidence for a CO group, and none for that of a $=NH^+$ group (cf. p. 3363).

The colour of an ethanolic solution of the indole (V; R = OMe) is unaffected by the addition of aqueous sodium hydroxide, but that of a similar solution of the 6-hydroxyindole (V; R = OH) becomes a much deeper yellow, undoubtedly by resonance between the anion provided by the hydroxyl group in (V; R = OH) and the anion (VII).

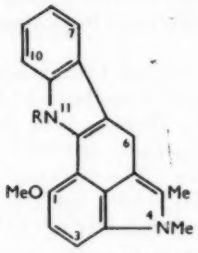


An ethanolic solution of the 6-hydroxy-indole (V; R = OH) gives a green colour with ferric chloride, whereas that of the 6-methoxyindole is unaffected.

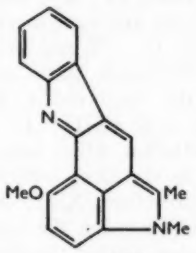
[10] Grob and Payot, *Helv. Chim. Acta*, 1953, **36**, 839.

The phenylhydrazone of the 6-methoxyindole (V; R = OMe) readily underwent indolisation in boiling ethanolic hydrogen chloride, giving an orange hydrochloride of composition $[C_{20}H_{17 \text{ or } 19}ON_2]Cl$, which was readily converted into the corresponding hydriodide, thiocyanate, and picrate. An aqueous solution of the hydrochloride, when made alkaline, deposited a reddish solid which darkened rapidly in the air or in a vacuum, decomposed more readily on attempted crystallisation, and gave a tar on attempted sublimation in a vacuum. Consequently structural identification was dependent on a study of the salts, the low solubility of which in hot solvents prevented recrystallisation.

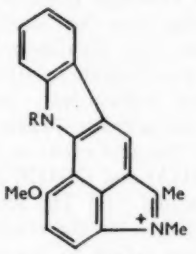
Now normal indolisation of the above phenylhydrazone would give 6 : 11-dihydro-1-methoxy-4 : 5-dimethyl-4*H*-indolo[4, 3-*ab*]carbazole (VIII; R = H) which, having two



(VIII)



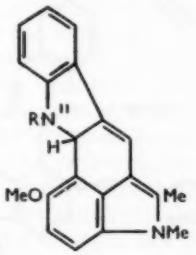
(IX)



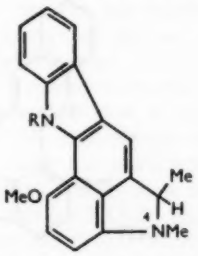
(X)

true indole groups, should be neutral. Several phenylhydrazones described in earlier papers in this series [1, 11, 12, 2] have, however, given yellow ψ-indoles, which have united readily with acids and with methyl iodide to give colourless salts. The phenylhydrazone of the 6-methoxyindole (V; R = OMe) could, therefore, have given 1-methoxy-4 : 5-dimethyl-4*H*-indolo[4, 3-*ab*]carbazole (IX) which with acids and with methyl iodide would have given the cations (X; R = H) and (X; R = Me) respectively. The analysis of the above hydrochloride and other salts did not differentiate sharply between a salt of the true indole (VIII) and that of the ψ-indole (IX).

The evidence against the ψ-indole structure (X; R = H) for the hydrochloride is twofold. (*a*) The infrared spectrum of this salt showed no band in the 2·95 μ region, indicating absence of an >NH group. (*b*) The methylphenylhydrazone of the 6-methoxyindole (V; R = OMe) underwent indolisation under similar conditions to give a crystalline orange hydrochloride having closely similar properties to those of the previous hydrochloride. The presence of the *N*-methyl group must now prevent ψ-indole formation of type (IX), but the normal indole (VIII; R = Me) should again be neutral.



(XI)



(XII)

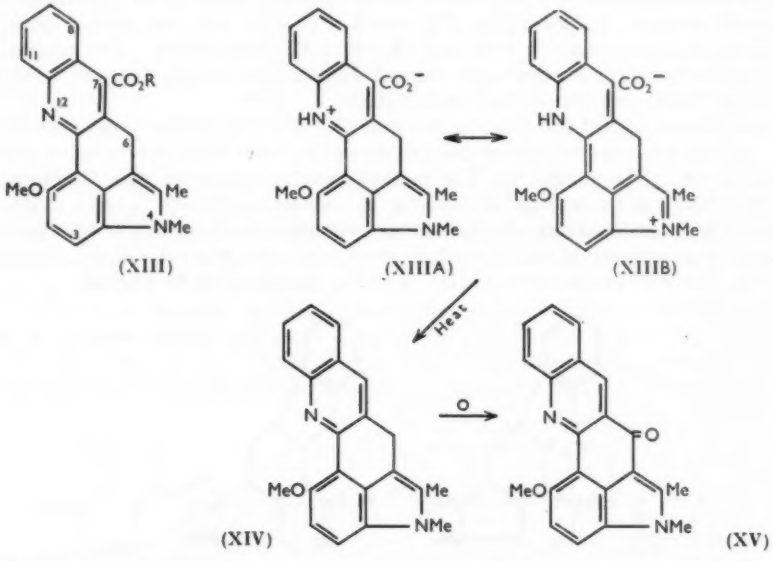
It is possible that the indole (VIII; R = H or Me) has undergone isomeric change, whereby the indole (XI) or (XII) might be formed: the fundamental difference between these two isomers is that in (XI) the upper, and in (XII) the lower, indole system has

[11] Mann and Smith, *J.*, 1951, 1898.
[12] Almond and Mann, *J.*, 1952, 1870.

adopted the indoline structure. Consequently salt formation would now occur by proton addition to the 11-nitrogen atom in (XI) and to the 4-nitrogen atom in (XII), giving in the hydrochlorides of the indoles (XI; R = H) and (XII; R = H), a $>NH_2^+$ and a $\equiv NH^+$ group respectively. The infrared spectrum of the hydrochloride again gives apparently decisive evidence, for it shows no absorption in the 3·85—3·90 μ region, where a $\equiv NH^+$ group usually gives broad absorption, but does show marked absorption in the 3·17—3·27 μ region, which would be expected if a $>NH_2^+$ group were present. (The absorption at 3·17—3·27 μ is quite distinct from a separate band at 3·4 μ due to CH groups.) The available evidence, therefore, strongly indicates that these indole derivatives have the structure (XI).

By the Pfitzinger reaction the indole (V; R = OMe) gave a series of quinolino-derivatives having some clear similarities to, and some marked differences from, those obtained, for example, from the oxo-amine (I; R = Ph and Me).[1,2]

When an ethanolic solution of the indole, isatin, and potassium hydroxide was boiled, acidification subsequently gave the deep red 4 : 6-dihydro-1-methoxy-4 : 5-dimethylindolo[3, 4-*bc*]acridine-7-carboxylic acid (XIII; R = H). There is little doubt, however, that this acid exists as a zwitterion, which forms a resonance hybrid to which the forms (XIIIA) and (XIIIB) provide the chief contributions. The evidence of this can be summarised: (*a*) The formal structure (XIII; R = H) should not give rise to an intense colour. On the other hand, although the quinonoid character of (XIIIB) would impart some colour to the resonance hybrid, the chief source of colour arises from the fact that (XIIIA) and (XIIIB) are two canonical forms of a cyanine type of compound. The acid, moreover, forms a bright yellow sodium salt (XIII; R = Na), in which, although some charge separation undoubtedly occurs, this cyanine structure is absent. (*b*) The infrared spectrum of the acid shows a strong and a rather weaker band at 6·21 and 6·33 μ



respectively, due to the CO_2^- group (cf. Braunholtz and Mann [2, 13]). (*c*) The ultraviolet spectra of the acid in ethanol, and in ethanol containing hydrochloric acid, are very similar, and differ markedly from that in ethanol containing sodium hydroxide (Fig. 2). This is to be expected, because the hydrochloride of the acid will give a cation having canonical

[13] Braunholtz and Mann, *J.*, 1955, 393.

forms identical with (XIIIA) and (XIIIB), apart from the conversion of the CO_2^- into the CO_2H group: the sodium salt (XIII; R = Na) will have a fundamentally different structure.

The acid (XIIIA–B) when heated in a vacuum underwent decarboxylation to form the orange-yellow amine (XIV), m. p. 156—158°, which gives red salts with acids. These colours are also to be expected, for the amine (XIV) has essentially the same structure as (XIII), with, however, the CO_2R group replaced by hydrogen, whereas the red salts of the amine will have a cation having contributing forms identical with (XIIIA–B) with the CO_2^- group replaced by hydrogen. The absorptions of solutions of the amine (XIV) in ethanol and hydrochloric acid are shown in Fig. 3.

The quinolino-amines similar in type to (XIV) but derived from the keto-amines (I; R = Ph and Me) [1,2] and from 1-oxojulolidine [11] underwent ready atmospheric oxidation, particularly in benzene solution, to give a cyclic amide. The amine (XIV) underwent this type of oxidation only when treated in cold acetone with potassium permanganate, furnishing the bright yellow **4**:6-dihydro-1-methoxy-**4**:5-dimethyl-6-oxoindolo-[3, 4-*bc*]acridine (XV), m. p. 220—223°. The infrared spectrum of this compound showed bands at 6·09 and 6·17 μ, indicating a conjugated $\rangle$CO group. The compound did not give a 2:4-dinitrophenylhydrazone, which accords with its structure as a vinylogue of an acid amide: it gave a crystalline dull orange hydriodide.

The above results are in general similar to those obtained with earlier analogous compounds. When, however, concentrated hydrochloric acid was added to the cold reddish-purple aqueous solution of the acid (XIIIA–B), the hydrochloride of the acid separated as a similarly coloured gel, which was very difficult to manipulate. On warming, the gel dissolved, the colour of the solution changed, and the orange-brown hydrochloride of the isomeric acid, **4**:7-dihydro-1-methoxy-**4**:5-dimethylindolo[3, 4-*bc*]acridine-7-carboxylic acid (XVI) crystallised. It is unfortunate that the free acid (XVI), obtained in aqueous solution by treating the hydrochloride with alkali (1 equiv.), was too soluble to be isolated, and its low solubility in organic solvents prevented its satisfactory extraction: consequently its properties could not be studied directly. There is little doubt that the essential difference between the two acids is that the isomeric acid (XVI) has undergone the allylic transformation: this is supported by previous analogous examples,[2, 11, 13] and more strongly by the properties of the corresponding amine and its oxidation product described below.

It is uncertain, however, whether this acid exists as a zwitterion, although this structure in indicated by the low solubility in organic solvents. Furthermore, its hydrochloride should show resonance corresponding to (XVIA–B), but the addition of aqueous sodium hydroxide to the orange aqueous or ethanolic solutions produces only a deeper orange-brown colour, and the ultraviolet spectra of solutions of the hydrochloride in 0·1N-aqueous hydrochloric acid and 0·1N-aqueous sodium hydroxide are closely similar (Fig. 4) in strong contrast to the marked differences of the spectra of the acid (XIII; R = H) in these conditions. Consequently the relative contributions of the forms (XVIA and B) in the hydrochloride are also uncertain: the above evidence indicates strongly, however, that the form (XVIA) makes almost an exclusive contribution to the hydrochloride, and that, therefore, the hydrochloride and the sodium salt have fundamentally the same structure.

When, however, this hydrochloride was heated in a vacuum, hydrogen chloride and carbon dioxide were evolved with the formation of the yellow amine (XVII), m. p. 239—240°, isomeric with the amine (XIV). The amine (XVII) gave a deep red solution in hydrochloric acid, and formed a dark maroon-coloured crystalline hydriodide: it is clear, therefore, that the cation present in salts of the amine receives contributions from two canonical forms similar to (XVIA–B) with the CO_2H group replaced by a hydrogen atom, and thus shows the familiar cyanine-like resonance. The absorption of solutions of this amine (XVII) in ethanol and 0·1N-hydrochloric acid are shown in Fig. 5, for comparison with those of the isomeric amine (XIV) in Fig. 3.

Oxidation of the amine (XVII) with permanganate in acetone gave the yellow 4 : 7-dihydro-1-methoxy-4 : 5-dimethyl-7-oxoindolo[3, 4-*bc*]acridine (XVIII), m. p. 305—308°, isomeric with the 6-oxo-derivative (XV). The infrared spectrum of the compound (XVIII) showed a single band at 6·15 μ, again indicating a conjugated >CO group.

FIG. 2. 4 : 6-*Dihydro-1-methoxy-4 : 5-dimethylindolo*[3, 4-bc]*acridine-7-carboxylic acid* (XIII; R = H), (*A*) *in ethanol* (2·075 *mg.*/50 *c.c.*); (*B*) *in ethanol* (1·610 *mg.*/50 *c.c.*) *containing* 0·25 *c.c. of* 10% *aqueous* HCl; (*C*) *in* 10% *aqueous sodium hydroxide* (1·000 *mg.*/50 *c.c.*).

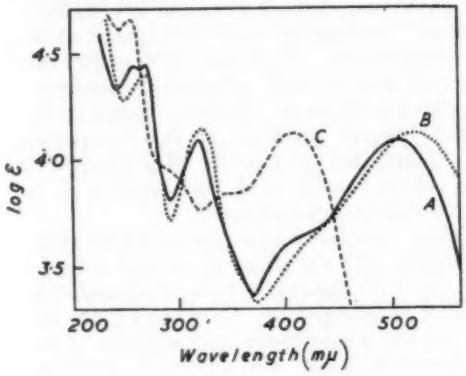
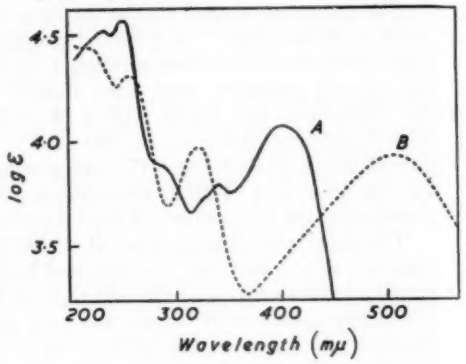


FIG. 3. 4 : 6-*Dihydro-1-methoxy-4 : 5-dimethylindolo*[3, 4-bc]*acridine* (XIV), (*A*) *in ethanol* (0·840 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous* HCl (0·930 *mg.*/50 *c.c.*).



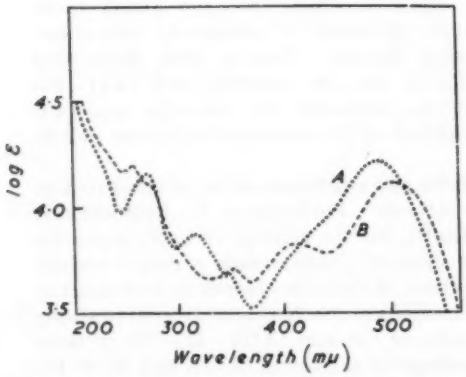


FIG. 4. *Hydrochloride of* 4 : 7-*dihydro-1-methoxy-4 : 5-dimethylindolo*[3, 4-bc]*acridine-7-carboxylic acid* (XVI), (*A*) *in* 0·1N-*aqueous* HCl (1·900 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous sodium hydroxide* (1·320 *mg.*/50 *c.c.*).

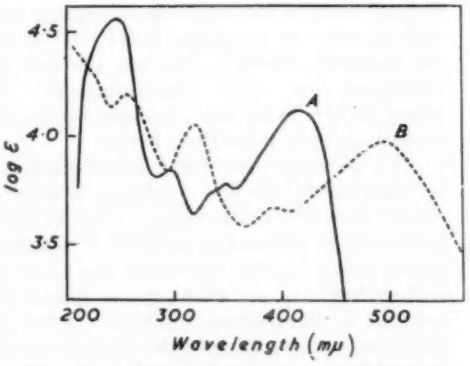


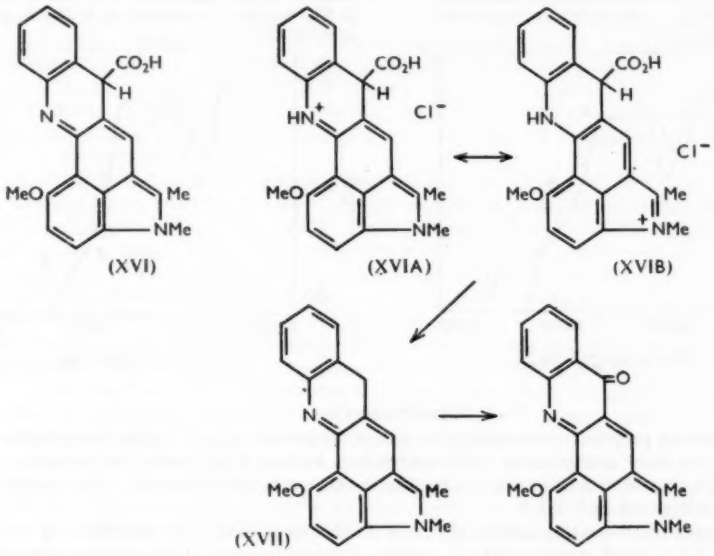
FIG. 5. 4 : 7-*Dihydro-1-methoxy-4 : 5-dimethylindolo*[3, 4-bc]*acridine* (XVII), (*A*) *in ethanol* (0·815 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous* HCl (0·985 *mg.*/50 *c.c.*).

The compound (XVIII), like the isomeric (XV), did not react with 2 : 4-dinitrophenylhydrazine, and gave a dark orange crystalline hydriodide.

The general structures of the isomeric bases (XIV) and (XVII), apart from the position of the " allylic " hydrogen, are so closely similar that their ultraviolet spectra in ethanol are also similar: the spectra in 0·1N-aqueous hydrochloric acid are correspondingly similar, although each is markedly different from that of the parent amine (Figs. 3, 5).

On the other hand, the spectra of the two isomeric oxidation compounds (XV) and (XVIII) in each of the above solvents are all closely alike (Figs. 6, 7), indicating that protonation leaves each compound essentially unchanged in structure.

In previous examples of bases similar to (XIV), namely, quinolino(2′ : 3′-1 : 2)-juloline,[11] 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline,[2] and diquinolino-(2′ : 3′-1 : 2)(3″ : 2″-5 : 6)juline,[13] the isomeric base, when heated in a vacuum, underwent conversion into the original base with sublimation. Our present bases (XIV) and (XVII) are exceptional in that each sublimes unchanged, and interconversion of the bases, by heating them with acids or by sublimation, has not been detected.



The absence of this interconversion of these two bases is not, however, unexpected. Braunholtz and Mann [2] have suggested that the mechanism of the acid-catalysed conversion of 1 : 2-dihydro- into 1 : 4′-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline consists essentially of two steps: (i) proton migration from the 1′- to the 1-nitrogen atom: the positive pole on the latter atom, being adjacent to the allylic methylene group, makes the hydrogen atom of this group more mobile, and catalyses step (ii), in which a proton migrates from position 2 to position 4′. This mechanism was supported by the fact that isomerisation of the corresponding 1-phenyl derivative was very sluggish, owing to the very weakly basic properties of the :NPh group.

In the base (XIV), however, the NMe group in position 4 is not only very feebly basic, but it is separated by a much longer chain from the 12-nitrogen atom. The comparable migration of the proton from the 12 to the 4-nitrogen atom would, therefore, be negligible, and the suggested mechanism of isomerisation could not apply to the base (XIV).

It is noteworthy that many attempts made to prepare 1 : 3 : 4 : 5-tetrahydro-6-methoxy-1 : 2-dimethyl-4 : 5-dioxobenz[*cd*]indole by the oxidation (direct or indirect) of the 4-methylene group in the 6-methoxyindole (V; R = OMe) group failed. Selenium dioxide under various conditions either left the indole unchanged or caused considerable decomposition: the application under the usual conditions of nitrous acid, pentyl nitrite, *p*-nitrosophenol, or *p*-nitrosodimethylaniline, in the hope of obtaining the oxime or anil in the 4-position for subsequent hydrolysis, gave intractable products. Further, the

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ketone (V; R = OMe) did not appear to undergo condensation, with or without subsequent indolisation, with 1-amino-1 : 2 : 3 : 4-tetrahydroquinoline.

In view of the fact that our quinolinoindoles have a ring system approaching that of lysergic acid, the acid (XIIIA–B), the hydrochloride (XVIA–B), and the amines (XIV) and (XVII) were kindly tested by Imperial Chemical Industries Limited (Pharmaceuticals Division) for anti-inflammatory action against egg-albumin-induced œdema in mice. The first three compounds were inactive and the last showed slight activity.

FIG. 6. 4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethyl*-6-*oxoindolo*[3, 4-bc]*acridine* (XV), (*A*) *in ethanol* (1·170 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous* HCl (0·875 *mg.*/50 *c.c.*).

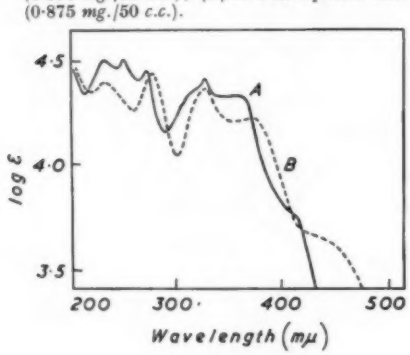
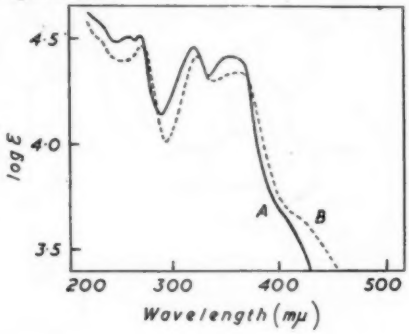


FIG. 7. 4 : 7-*Dihydro*-1-*methoxy*-4 : 5-*dimethyl*-7-*oxoindolo*[3, 4-bc]*acridine* (XVIII), (*A*) *in ethanol* (1·380 *mg.*/50 *c.c.*); (*B*) *in ethanol* (1·535 *mg.*/50 *c.c.*) *containing* 0·25 *c.c. of* 10% *aqueous* HCl.



EXPERIMENTAL

The compounds prepared were colourless unless otherwise stated. Many compounds gave consistent m. p.s only if the latter were determined in sealed evacuated tubes (denoted by " E.T."), which in addition often had to be immersed just below the m. p. : the temperature of immersion is denoted as " T.I.".

3-2′-*Cyanoethyl*-1 : 2-*dimethylindole* (IV; R = H, R′ = CN).—A mixture of 1 : 2-dimethylindole (5 g.), vinyl cyanide (3·4 g.), powdered copper acetate (1·7 g.) and copper powder (1·7 g.) was heated in a sealed tube for 12 hr. at 120—130°. The cold solution was filtered, neutralised with aqueous potassium carbonate, and extracted with chloroform. After drying, removal of the chloroform left a residue which, recrystallised from aqueous ethanol, gave the crystalline *indole* (IV; R = H, R = CN), m. p. 108—109° (Found : C, 78·6; H, 7·4; N, 14·2. $C_{13}H_{14}N_2$ requires C, 78·7; H, 7·1; N, 14·1%) (3·5 g., 51%). Cyanoethylation was not achieved when a mixture of the indole and vinyl cyanide was (*a*) heated with sodium methoxide at 130—140° for 15 hr., (*b*) dissolved in glacial acetic acid and boiled under reflux for 6 hr., (*c*) dissolved in dioxan containing benzyltrimethylammonium hydroxide and similarly boiled.

3-2′-*Carboxyethyl*-1 : 2-*dimethylindole* (IV; R = H, R′ = CO_2H).—(*A*) A mixture of 1 : 2-dimethylindole (9·2 g.) and β-propiolactone (9·2 g.) was heated with stirring at 150° for 3 hr., cooled, and extracted with cold ether. Polymerised propiolactone solidified to a pink powder which was filtered from the ether solution. The latter was extracted with 10% aqueous potassium hydroxide (2 × 50 c.c.), which on acidification deposited the *acid* (IV; R = H, R′ = CO_2H), m. p. 153—154° (from aqueous ethanol) (Found : C, 72·0; H, 7·2; N, 6·6. $C_{13}H_{15}O_2N$ requires C, 71·8; H, 7·0; N, 6·5%) : 7 g., 51%. (*B*) The indole (IV; R = H, R′ = ·CN) was hydrolysed by boiling 10% aqueous potassium hydroxide, and the clear cold solution on acidification gave the above acid.

The following experiment is noteworthy among the many attempts to achieve cyclisation. A solution of the acid (IV; R = H, R′ = CO_2H) (3 g.) in acetic anhydride (125 c.c.) containing potassium cyanide (0·02 g.) was boiled under reflux for 20 hr., and the anhydride then distilled off. An ether extract of the residue, when washed with dilute alkali, dried and evaporated, left a crystalline product showing faint ketonic properties. Three recrystallisations from ethanol gave the *anhydride* of the above acid, needles, m. p. 117—118° (Found : C, 75·1:

H, 6·8; N, 6·8. $C_{26}H_{28}O_3N_2$ requires C, 75·0; H, 6·8; N, 6·7%) : it underwent ready hydrolysis to the acid.

The ethanolic mother-liquors on evaporation gave a residue, which was added to 5% aqueous sodium hydroxide, boiled for 15 min., cooled, and extracted with ether. This extract on evaporation gave a small quantity of an uncrystallisable ketonic oil. With ethanolic 2 : 4-dinitrophenylhydrazine, this deposited orange-red 1 : 3 : 4 : 5-*tetrahydro*-1 : 2-*dimethyl*-5-*oxobenz*[cd]*indole* 2 : 4-*dinitrophenylhydrazone monoethanolate*, m. p. 237—239° (decomp.) (E.T.) after washing with boiling ethanol (Found : C, 58·8; H, 5·1; N, 16·6. $C_{19}H_{17}O_4N_5,C_2H_6O$ requires C, 59·2; H, 5·45; N, 16·5%).

The following experiments (*A–C*) were directed to the preparation of 1-ethyl-2 : 5 : 7-trimethylindole, in which the 4-position should have marked activity.

(*A*) N-*Ethyl*-2 : 4-*dimethylaniline and its Hydrobromide*.—2 : 4-Dimethylaniline (121 g.) and ethyl bromide (109 g., 1 mol.) were set aside together for 3 days. The crystalline mass was then stirred with acetone and filtered, furnishing the *hydrobromide*, needles, m. p. 151—152° after crystallisation from acetone (1·5 l.) (Found : C, 52·2; H, 6·8; N, 6·1. $C_{10}H_{15}N,HBr$ requires C, 52·2; H, 7·0; N, 6·1%) : 131·5 g., 57%. Basification and ether-extraction then gave the *aniline*, b. p. 57·5°/0·4 mm. (Found : C, 80·4; H, 10·1; N, 9·45. $C_{10}H_{15}N$ requires C, 80·5; H, 10·1; N, 9·4%).

(*B*) N-*Ethyl*-2 : 4-*dimethyl*-N-*nitrosoaniline*.—A mixture of the aniline (110 c.c.), concentrated hydrochloric acid (110 c.c.), and crushed ice (300 g.) was stirred with external cooling whilst a solution of sodium nitrite (51·5 g., 1 mol.) in water (185 c.c.) was added during 10 min., stirring being continued for 1 hr. Extraction with ether and removal of solvent gave the nitrosamine as a yellow oil (112 g., 85%), which was not further purified.

(*C*) as.-*Ethyl*-2 : 4-*dimethylphenylhydrazine*.—Attempted reduction of the nitrosamine with zinc and acetic acid gave solely the original aniline. Consequently, lithium aluminium hydride (12 g.) in ether (400 c.c.) was placed in a 3-necked flask (2 l.) fitted with a stirrer, reflux condenser, and dropping-funnel. The ether was stirred whilst a solution of the nitrosamine (55 g., 1 mol.) in ether (100 c.c.) was slowly added, the reaction causing the mixture to boil. After 1 hour's stirring wet ether (200 c.c.) was added, and then, very cautiously, 30% aqueous sodium hydroxide (75 c.c.). The ethereal layer was separated, united with an ethereal extract of the aqueous layer, dried, and distilled. The *hydrazine* was obtained as an oil, b. p. 73°/0·4 mm. (Found : C, 73·5; H, 9·6; N, 16·8. $C_{10}H_{16}N_2$ requires C, 73·1; H, 9·8; N, 17·1%) (35 g., 69%). This procedure gave more satisfactory results than when conversely the ethereal hydride was added to the nitrosamine, which Poirier and Benington [14] recommend for such reductions.

Acetone (4·4 c.c.) was added to a solution of the hydrazine (10 g., 1 mol.) in 40% aqueous acetic acid (10 c.c.), which when shaken became warm as the hydrazone (12 g., 96%) separated as an upper layer. This was separated and dried, but attempts to convert it into the indole failed and its use was abandoned.

N-*Methyl*-N-*nitroso*-p-*anisidine*.—Methyl sulphate (1425 c.c.) was run into a stirred solution of *p*-anisidine (1845 g.) in methanol (1 l.) at such a rate that it boiled gently. The solution was heated at 100° for 2 hr., and the methanol then distilled off. The cold residue was treated with a solution of sodium hydroxide (750 g.) in water (1·5 l.), and the oil collected : a further quantity was obtained by ether-extraction of the aqueous layer. The crude *N*-methyl-*p*-anisidine was dissolved in concentrated hydrochloric acid (2·4 l.) containing ice (5 kg.) in a 27 l. earthenware vessel. A solution of sodium nitrite (1·2 kg.) in water (1·5 l.) was slowly run in below the surface of the stirred solution, with addition of ice to keep the temperature below 10°. After 1 hr., the yellow solid nitrosamine was collected, thoroughly washed with water, and dried; it had m. p. 42—44° (771 g., 31%). King and Robinson [15] give m. p. 45—46° for the recrystallised compound.

N-p-*Methoxyphenyl*-N-*methylhydrazine*.—The nitrosamine, when reduced with lithium aluminium hydride as described above, gave the hydrazine, b. p. 139—142°/13 mm., in 30% yield. For large-scale work, a solution of the nitrosamine (166 g.) in glacial acetic acid (320 c.c.) was added during 3—4 hr. to a stirred mixture of zinc dust (480 g.) in 50% aqueous ethanol (600 c.c.) kept at 10—20°. After 1 hr. the mixture was warmed to 60°, filtered, made strongly alkaline with 30% aqueous sodium hydroxide, and extracted with ether. The dried extracts

[14] Poirier and Benington, *J. Amer. Chem. Soc.*, 1952, **74**, 3192.
[15] King and Robinson, *J.*, 1933, 271.

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from two preparations were united, the ether removed, and the product, when distilled at 12 mm., gave the fractions: (*a*) b. p. 131—135°, 119 g.; (*b*) b. p. 137—141°, 13 g.; and (*c*) b. p. 143—146°, 133 g. The colourless fractions (*a*) and (*b*) were *N*-methyl-*p*-anisidine and crystallised when set aside. The brown fraction (*c*) was the required hydrazine (49%).

*5-Methoxy-***1** : **2***-dimethylindole* (III; R = OMe).—A mixture of the hydrazine (152 g.), acetone (80 c.c., 1·1 mols.), and acetic acid (5 c.c.) was heated for 2 hr., water separating as the hydrazone was formed. Without purification, the cold product was added to ethanol (1·5 l.) saturated with hydrogen chloride, which was boiled under reflux for 2 hr. and poured into water (10 l.). The dark tarry precipitate was collected, and the filtrate extracted with chloroform. The united solid and extract when distilled gave the *indole* (III; R = OMe) as a pale yellow oil, b. p. 134—137°/0·3 mm., m. p. 76·5—77·5° (from ethanol) (Found: C, 75·2; H, 7·45; N, 8·1. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5; N, 8·0%) (64 g., 37%). The distillation left a considerable dark residue.

In an attempted alternative synthesis, monobromoacetone was added to *N*-methyl-*p*-anisidine in ethanol containing sodium hydrogen carbonate at 50°. Working up gave *p*-methoxyphenyl-*N*-methylaminopropanone, b. p. 175°/12 mm., which when heated with *N*-methyl-*p*-anisidine and a trace of hydrochloric acid gave 5-methoxy-1 : 3-dimethylindole, m. p. 59—60·5°, after crystallisation from ethanol (lit.,[16] m. p. 60—61°).

3 - **2′***-Cyanoethyl-5-methoxy-***1** : **2***-dimethylindole* (IV; R = OMe, R′ = CN).—This compound was prepared by Braunholtz and Mann's method,[17] a mixture of the indole (III; R = OMe) (87·5 g.), vinyl cyanide (36 c.c., 1·1 mols.), acetic acid (30 c.c.), and cuprous chloride (5 g.) being heated under reflux for 6 hr. and then poured into aqueous ammonia. The solid precipitate, when thoroughly washed with ammonia and water and crystallised from ethanol, afforded the *indole*, m. p. 124·5—125·5° (Found: C, 73·7; H, 6·85; N, 12·5. $C_{14}H_{16}ON_2$ requires C, 73·65; H, 7·05; N, 12·3%): 96 g., 84%.

3-2′*-Carboxyethyl-5-methoxy-***1** : **2***-dimethylindole* (IV; R = OMe, R′ = CO_2H).—(*A*) A mixture of the indole (III; R = OMe) (10 g.) and β-propiolactone (5 c.c., 1·4 mols.) was heated at 150° for 4 hr., cooled, and extracted with ether. The ethereal solution was filtered to remove polymerised lactone, and extracted with dilute aqueous sodium hydroxide. Evaporation of of the ether gave unchanged indole (3·2 g.). Acidification of the alkaline extract gave an oil which solidified, and when recrystallised from 50% aqueous ethanol gave the *acid*, m. p. 119—120·5° (Found: C, 68·0; H, 6·7; N, 5·6. $C_{14}H_{17}O_2N$ requires C, 68·0; H, 6·9; N, 5·7%) (6·7 g., 70% after allowance for recovered indole). (*B*) Solutions of the indole (IV; R = OMe, R′ = CN) (114 g.) in ethanol (500 c.c.) and of sodium hydroxide (120 g.) in water (1·2 l.) were mixed and boiled under reflux for 7 hr.; after the ethanol had been distilled off, acidification of the cold solution with concentrated hydrochloric acid precipitated the acid (119 g., 96%).

1 : **3** : **4** : **5***-Tetrahydro-6-hydroxy-***1** : **2***-dimethyl-5-oxobenz*[cd]*indole* (V; R = OH).—A mixture of the indole (IV; R = OMe, R′ = CO_2H) (20 g.), concentrated sulphuric acid (100 c.c.), and phosphoric acid (100 c.c.) was heated at 165° ± 5° for 30 min., allowed to cool slightly, and poured into water (1·5 l.). After 1 hr., the brown precipitate was collected and recrystallised from ethanol, giving the yellow *benzindole* (V; R = OH), m. p. 142—144° (Found: C, 72·2; H, 5·7; N, 6·55%; *M*, in boiling ethanol, 230. $C_{13}H_{13}O_2N$ requires C, 72·4; H, 6·0; N, 6·5%; *M*, 215) (4·3 g., 32% after allowance for recovered acid).

The aqueous solution was extracted with chloroform, which was then extracted with aqueous sodium carbonate. Acidification of the carbonate extract precipitated **3-2′***-carboxyethyl-5-hydroxy-***1** : **2***-dimethylindole* (IV; R = OH, R′ = CO_2H), m. p. 147—149° after recrystallisation from water (Found: C, 67·3; H, 6·6; N, 6·1. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5; N, 6·0%) (4·3 g., 23%). This acid also underwent cyclisation to the benzindole (V; R = OH) under the above conditions.

The acid gave a transient purple colour with ferric chloride, and was readily converted into the indole (IV; R = OMe, R′ = CO_2H) by methyl sulphate and aqueous sodium hydroxide. The acid, when added to aqueous sodium hydroxide and treated with toluene-*p*-sulphonyl chloride in acetone, gave **3-2′***-carboxyethyl-***1** : **2***-dimethyl-6-toluene-*p*-sulphonyloxyindole* (IV; R = $O{\cdot}SO_2{\cdot}C_7H_7$, R′ = CO_2H), m. p. 199—200·5° (Found: C, 62·4; H, 5·6; N, 3·7. $C_{20}H_{21}O_5NS$ requires C, 62·0; H, 5·5; N, 3·6%).

Derivatives of the **6***-Hydroxy-benz*[cd]*indole* (V; R = OH).—(1) A solution of the indole

[16] Janetzky, Verkade, and Lieste, *Rec. Trav. chim.*, 1946, **65**, 199.
[17] Braunholtz and Mann, *J.*, 1953, 1817.

(0·5 g.), phenylhydrazine (0·5 c.c.), and acetic acid (0·2 c.c.) in ethanol (15 c.c.) was boiled for 1 hr., and on cooling deposited the crystalline *phenylhydrazone* (0·66 g., 95%), initially bright yellow, but separating from benzene as almost colourless crystals, m. p. 238—239° (E.T.; T.I. 232°) (Found: C, 74·5; H, 6·0; N, 13·6. $C_{19}H_{19}ON_3$ requires C, 74·7; H, 6·3; H, 13·75%). (2) A solution of the indole in acetic acid and acetic anhydride, when heated and poured into water, gave the yellow *6-acetoxy-derivative* (V; R = OAc), m. p. 157·5—158·5° (from ethanol) (Found: C, 70·0; H, 5·8; N, 5·7. $C_{15}H_{13}O_3N$ requires C, 70·0; H, 5·9; N, 5·45%). This gave a very pale cream *phenylhydrazone*, m. p. 224·5—225·5° (E.T.; T.I. 219°) (Found: C, 72·7; H, 6·2; N, 12·1. $C_{21}H_{21}O_2N_3$ requires C, 72·65; H, 6·1; N, 12·1%). (3) The indole gave a yellow *6-toluene-p-sulphonyloxy-derivative* (V; R = O·SO_2·C_7H_7), m. p. 208—209°, after crystallisation from ethanol (Found: C, 65·4; H, 5·3; N, 3·6. $C_{20}H_{19}O_4NS$ requires C, 65·05; H, 5·2; N, 3·8%). This gave an orange 2 : *4-dinitrophenylhydrazone*, m. p. 265° (E.T.; T.I. 255°) after crystallisation from much xylene (Found: C, 56·7; H, 3·95; N, 12·45. $C_{26}H_{23}O_7N_5S$ requires C, 56·8; H, 4·2; N, 12·75%). (4) A hot ethanolic solution of the indole, when treated with ethanol saturated with hydrogen chloride, became amber in colour and on cooling deposited green crystals, apparently of a very unstable hydrochloride. A sample recrystallised from ethanol regenerated the pure indole, m. p., mixed and unmixed, 142°. Another sample was collected and washed on the filter with ethanolic hydrogen chloride, but, in spite of being dried over calcium chloride at atmospheric pressure, it underwent very considerable dissociation although it retained the green colour and had m. p. 153—154° (Found: C, 71·0; H, 6·3. Calc. for $C_{13}H_{13}O_2N$,HCl: C, 62·3; H, 5·6. Calc. for $C_{13}H_{13}O_2N$: C, 72·4; H, 6·0%).

1 : 3 : 4 : 5-*Tetrahydro-6-methoxy-1* : *2-dimethyl-5-oxobenz*[cd]*indole* (V; R = OMe).—The following were the only conditions discovered under which the 6-hydroxy-compound could be methylated. The 6-hydroxybenzindole (V; R = OH) (23·6 g.) was dissolved in warm acetone (600 c.c.), and alternate additions of 30% aqueous sodium hydroxide (10 c.c.) and methyl sulphate (7 c.c.) were made with vigorous shaking until precipitation no longer occurred and a clear solution was obtained. (In a typical experiment, 15 such additions of each reagent, *i.e.*, *ca.* 10 mols. of sulphate, were required.) The solution was diluted with water (1 l.), the acetone distilled off, and the dull yellow product recrystallised from ethanol, giving the very pale yellow *6-methoxybenz*[cd]*indole* (V; R = OMe), m. p. 144—145° (Found: C, 73·25; H, 6·8; N, 6·3%; *M*, in boiling ethanol, 239. $C_{14}H_{15}O_2N$ requires C, 73·35; H, 6·6; N, 6·1%; *M*, 229).

Hydrochloride. A cold benzene solution of the indole (V; R = OMe), when treated with a stream of dry hydrogen chloride, became red and deposited well-formed deep red crystals of the hydrochloride. These crystals, when collected with a minimum of exposure to damp air and placed in an atmospheric or evacuated desiccator, slowly faded in colour, and when exposed to the air became sticky and reddish-black at the edges. A fresh sample was collected, washed on the filter with benzene–hydrogen chloride, pressed between filter-paper to absorb excess of benzene, and subjected at once to infrared absorptiometry and elementary analysis. The latter (Found: C, 12·15. Calc. for $C_{14}H_{15}O_2N$,HCl: Cl, 13·4%) does not differentiate between contamination with benzene or slight dissociation. The infrared spectrum, determined in a film pressed between sodium chloride plates, showed a broad OH band centred about 3308—3360 cm.$^{-1}$ (2·98—3·02 μ), but only a very feeble $>$CO band at 6·0 μ, and no indication of a $\equiv NH^+$ band in the 3·8—3·9 μ region. A small amount of Nujol was then rubbed in the film, which was again compressed. The spectrum still showed the broad OH band, but a moderately strong $>$CO band had now developed at 6·0 μ, and the film had become paler. A portion of the initial red crystals, when stirred with 5% aqueous sodium hydroxide, lost their red colour and deposited yellowish crystals, m. p. 138—140°, which after recrystallisation from ethanol gave the pale yellow 6-methoxyindole (V; R = OMe), m. p. and mixed m. p. 140—142°.

A warm ethanolic solution of this indole, when treated with ethanolic hydrogen chloride, became deep red but did not deposit crystals when chilled. It was taken to dryness in a vacuum desiccator, and the brittle deep red resin recrystallised from hot acetone to which just sufficient ethanolic hydrogen chloride was added to give a complete solution, which when cooled and stirred slowly deposited a fine brown microcrystalline powder, m. p. 207° (decomp.) (T.I. 200°) when dried over calcium chloride in an atmospheric desiccator (Found: C, 63·1; H, 6·2; N, 5·5; Cl, 13·5. $C_{14}H_{15}O_2N$,HCl requires C, 63·3; H, 6·0; N, 5·3; Cl, 13·4%). Although this compound appeared to be a *hydrochloride*, it differed from the authentic red salt in that (*a*) when exposed to the air it decomposed much more slowly, without becoming sticky, (*b*) when treated with 5% aqueous sodium hydroxide it gave only a dark sticky intractable gum. The

indole appeared, therefore, to have undergone some fundamental change during this treatment, and the nature of this brown salt was not further investigated.

The 6-methoxybenz[*cd*]indole (V; R = OMe) readily gave a *phenylhydrazone*, almost colourless plates, m. p. 150—150·5° (from ethanol) (Found: C, 75·4; H, 6·3; N, 13·2. $C_{20}H_{21}ON_3$ requires C, 75·2; H, 6·6; N, 13·15%), and a yellow *methylphenylhydrazone*, m. p. 131—132° (E.T.; T.I. 127°) (from ethanol) (Found: C, 75·9; H, 7·1; N, 12·55. $C_{21}H_{23}ON_3$ requires C, 75·65; H, 6·95; N, 12·6%). The phenylhydrazone had high stability and was unchanged in appearance and m. p. after 2 years, whereas the methylphenylhydrazone had darkened considerably after 4 months.

Indolo-derivatives.—Since these compounds were isolated only as salts, in which the position of the tautomeric hydrogen atom, although very probably that shown in (XI), is not quite certain, they will be considered for simplicity of reference and nomenclature to have the normal indolo-structure (VIII).

6 : 11-*Dihydro*-1-*methoxy*-4 : 5-*dimethyl*-4H-*indolo*[4, 3-ab]*carbazole* (VIII; R = H). The hydrazone (2 g.) of the benz[*cd*]indole (V; R = OMe) in ethanol (15 c.c.) was mixed with saturated ethanolic hydrogen chloride (15 c.c.), and heated under reflux for 3 hr., an orange solid separating meanwhile. The mixture was set aside overnight at 0°, and the solid, m. p. 296° (E.T.; T.I. 285°) (1·0 g.) collected. It dissolved readily in hot methanol, which on cooling deposited the orange yellow *hydrochloride* (Found, in two preparations: C, 70·7, 71·6; H, 5·4, 5·0; N, 8·7, 8·1. $C_{20}H_{18}ON_2,HCl$ requires C, 70·9; H, 5·65; N, 8·25%).

A methanolic solution of the hydrochloride, treated with aqueous sodium iodide, deposited the *hydriodide*, orange-yellow needles, m. p. 304° (decomp.) (E.T.; T.I. 300°) (Found: C, 56·2; H, 4·1; N, 6·65. $C_{20}H_{18}ON_2,HI$ requires C, 55·8; H, 4·45; N, 6·5%). The *thiocyanate*, similarly prepared, formed yellow needles, m. p. 279° (E.T.; T.I. 275°) (Found: C, 69·8; H, 4·75; N, 11·4. $C_{20}H_{18}ON_2,HCNS$ requires C, 69·8; H, 5·3; N, 11·6%). The *picrate* formed yellow needles, m. p. 240—241° (E.T.; T.I. 230°) (Found: C, 58·6; H, 3·85. $C_{26}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 58·7; H, 4·0%).

6 : 11-*Dihydro*-1-*methoxy*-4 : 5 : 11-*trimethyl*-4H-*indolo*[4, 3-ab]*carbazole* (VIII; R = Me) A mixture of the methylphenylhydrazone (1 g.), ethanol (7·5 c.c.) and saturated ethanolic hydrogen chloride (7·5 c.c.) was boiled under reflux for 5 hr., and the orange-coloured solution was concentrated, cooled, and diluted with acetone, the orange-yellow hydrochloride (0·45 g.), m. p. 343° (E.T.; T.I. 340°), slowly separating.

This salt was soluble in water, methanol and ethanol, and no suitable solvent for recrystallisation was found. The addition of alkali to its aqueous solution precipitated a reddish solid which rapidly darkened in air, and could not be sublimed in a vacuum. An aqueous solution of the hydrochloride, when treated with aqueous sodium iodide, deposited the orange *hydriodide hemihydrate*, m. p. 341° (E.T.; T.I. 339°) (Found: C, 55·75; H, 5·15. $C_{21}H_{20}ON_2,HI,0{\cdot}5H_2O$ requires C, 55·7; H, 4·9%). The orange *perchlorate*, similarly prepared, had m. p. 314° (E.T.; T.I. 310°) (Found: C, 61·2; H, 5·1; N, 6·8. $C_{21}H_{20}ON_2,HClO_4$ requires C, 60·5; H, 5·1; N, 6·7%).

Quinolino-derivatives.—**4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine*-7-*carboxylic acid*** (XIIIA–B). The 6-methoxy-indole (V; R = OMe) (4·5 g.), isatin (3·3 g.), and 40% aqueous potassium hydroxide (10 c.c.) were added to ethanol (40 c.c.), which was then boiled under reflux for 30 hr. The cold solution was filtered and diluted with water (80 c.c.) and acetic acid (10 c.c.), the yellow colour changing to a deep red. The solution was extracted with chloroform (3 × 30 c.c.), acetic acid (10 c.c.) being added after each extraction. The combined extracts were concentrated and diluted with light petroleum (b. p. 60—80°) (50 c.c.), a red solid, m. p. 160—163° (effervescence, E.T.; T.I. 150°) (5·8 g.), being precipitated. Recrystallisation from ethanol–acetone gave the *acid* (XIIIA–B), dull red crystals, m. p. 190° (effervescence, E.T.; T.I. 185°) (Found: C, 73·5; H, 4·95; N, 7·5. $C_{22}H_{16}O_3N_2$ requires C, 73·7; H, 5·05; N, 7·8%). The acid is readily soluble in water, but insoluble in chloroform and petroleum. It can, however, be extracted from its solution in dilute acetic acid by chloroform, almost certainly as its acetate, *i.e.*, the material of m. p. 160—163°, which then readily dissociates on recrystallisation: hence the above method of isolating the free acid.

The acid dissolved readily in 10% aqueous sodium hydroxide to give a yellow solution, which when set aside deposited bright yellow crystals of the *sodium salt* (XIII; R = Na) (Found: N, 7·1. $C_{22}H_{17}O_3N_2Na$ requires N, 7·35%).

4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine* (XIV). The above acid (1 g.)

when cautiously heated at 0·001 mm., the bath temperature rising finally to 300°, melted, effervesced, and then gave a sublimate of the orange-yellow *indoloacridine* (XIV), m. p. 156—158° (E.T.; T.I. 150°) (from ethanol) (Found: C, 80·15; H, 5·8; N, 8·95. $C_{21}H_{18}ON_2$ requires C, 80·25; H, 5·75; N, 8·9%) (0·4 g., 44%). When this decarboxylation was carried out with the initial precipitate, m. p. 160—163°, a gentle heating at 15 mm., during which acetic acid was liberated, preceded the stronger heating: the liberation of acetic acid confirms the identity of the precipitate as an unstable acetate.

The amine dissolves in dilute hydrochloric acid to give a red solution from which the hydrochloride could not be isolated: addition of ethanolic hydrogen chloride to an ethanolic solution of the base deposited the very hygroscopic red hydrochloride. Addition of dilute sulphuric acid to the ethanolic base deposited the dull red *hydrogen sulphate*, m. p. 232° (E.T.; T.I. 230°) (from aqueous ethanol) (Found: C, 61·0; H, 4·6. $C_{21}H_{18}ON_2,H_2SO_4$ requires C, 61·15; H, 4·9%). Hydriodic acid similarly gave the maroon *hydriodide*, m. p. 196—197° (decomp.) (T.I. 194°) (from aqueous ethanol) (Found: C, 57·05; H, 4·55; N, 6·3. $C_{21}H_{18}ON_2,HI$ requires C, 57·05; H, 4·35; N, 6·35%).

Oxidation. (*A*) The pale yellow solution of the base (XIV) in cold benzene was exposed to the air for 7 days, evaporation losses being made good from time to time. The reddish-brown solution was then evaporated, but the rust-coloured solid residue could not be crystallised, or sublimed in a vacuum.

(*B*) An acetone solution of potassium permanganate was added to a solution of the base (XIV) in acetone until, even when gently warmed, it retained a faint pink colour. The solid residue obtained by evaporation was then extracted with benzene (Soxhlet), the extract affording bright yellow *4 : 6-dihydro-1-methoxy-4 : 5-dimethyl-6-oxoindolo*[3, 4-bc]*acridine* (XV) (50%), m. p. 220—223° (E.T.; T.I. 215°) after recrystallisation from benzene (Found: C, 76·5; H, 4·7; N, 8·8. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9; N, 8·55%). This compound did not give a 2 : 4-dinitrophenylhydrazone. Its solution in dilute hydrochloric acid, when treated with aqueous sodium iodide, deposited the dull orange *hydriodide*, m. p. 296—299° (E.T.; T.I. 290°) (from aqueous ethanol) (Found: C, 55·3; H, 4·0; N, 6·4. $C_{21}H_{16}O_2N_2,HI$ requires C, 55·25; H, 3·75; N, 6·15%).

Isomerisation of the acid (XIIIA–B). The deep reddish-purple solution of this acid (3·8 g.) in warm water (130 c.c.), when stirred and treated with concentrated hydrochloric acid (30 c.c.), set to a gel, which on further warming gave a clear deep purple solution. When heated for a further 20 min., the solution became deep orange-brown, and when scratched deposited the orange-brown *4 : 7-dihydro-1-methoxy-4 : 5-dimethylindolo*[3, 4-bc]*acridine-7-carboxylic acid hydrochloride* (XVIA–B) (3·0 g., 78%), which, after recrystallisation from dilute hydrochloric acid, softens or melts at 160—170° (E.T.), resolidifies, and remelts at 235° (Found: C, 67·1; H, 5·2; N, 7·3. $C_{22}H_{18}O_3N_2,HCl$ requires C, 66·9; H, 4·9; N, 7·1%). This salt gave orange solutions in water or ethanol, the colour becoming a deeper orange on the addition of alkali: this behaviour is in marked contrast to that of the acid (XIIIA–B).

4 : 7-Dihydro-1-methoxy-4 : 5-dimethylindolo[3, 4-bc]*acridine* (XVII). The above hydrochloride (1 g.), when heated in a short-path sublimation apparatus at 0·001 mm., the bath-temperature rising to 280—300°, gave a sublimate of the yellow *base* (XVII) (0·6 g., 78%), m. p. 239—240° (E.T.; T.I. 238°) (from benzene) (Found: C, 80·0; H, 5·6; N, 9·1. $C_{21}H_{18}ON_2$ requires C, 80·25; H, 5·75; N, 8·9%). This base is very similar in appearance to the isomeric base (XIV), but is less soluble in ethanol and benzene: a mixture of the bases had m. p. 145—205°. The base (XVII) gave a deep red solution in dilute hydrochloric acid: addition of aqueous sodium iodide gave the dark maroon *hydriodide monohydrate*, m. p. 310—311° (E.T.; T.I. 305°) (from ethanol) (Found: C, 55·1; H, 4·3; N, 6·2. $C_{21}H_{18}ON_2,HI,H_2O$ requires C, 54·8; H, 4·6; N, 6·1%).

Attempts to obtain this base by boiling solutions of the base (XIV) in dilute hydrochloric acid, with subsequent basification, failed: no evidence that isomerisation occurred in these or similar conditions was obtained.

Oxidation. (*A*) The yellow solution of the base (XVII) in benzene was unchanged in colour after 5 days' exposure to the atmosphere, unchanged base being recovered.

(*B*) The base in acetone was oxidised with permanganate as described above. Extraction (Soxhlet) of the solid residue with benzene afforded *4 : 7-dihydro-1-methoxy-4 : 5-dimethyl-7-oxoindolo*[3, 4-bc]*acridine* (XVIII) (10%), which after vacuum-sublimation and recrystallisation from 2-methoxyethanol formed yellow crystals, m. p. 305—308° (E.T.; T.I. 280°)

XUM

(Found: C, 76·8; H, 5·0; N, 8·65. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9; N, 8·55%). It did not form a 2 : 4-dinitrophenylhydrazone. Addition of sodium iodide to its solution in hot dilute hydrochloric acid deposited the hygroscopic dull orange *hydriodide hemihydrate*, m. p. 336—338° (E.T.; T.I. 330°) (Found: C, 54·1; H, 3·9; N, 6·4. $C_{21}H_{16}O_2N_2,HI,0{\cdot}5H_2O$ requires C, 54·3; H, 3·9; N, 6·05%).

We are greatly indebted to Dr. C. Y. Almond for assistance in the preliminary stages of this work, to Imperial Chemical Industries Limited, Dyestuffs Division, for materials, and to Imperial Chemical Industries Limited (Pharmaceuticals Division) for therapeutic tests.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 13th*, 1957.]

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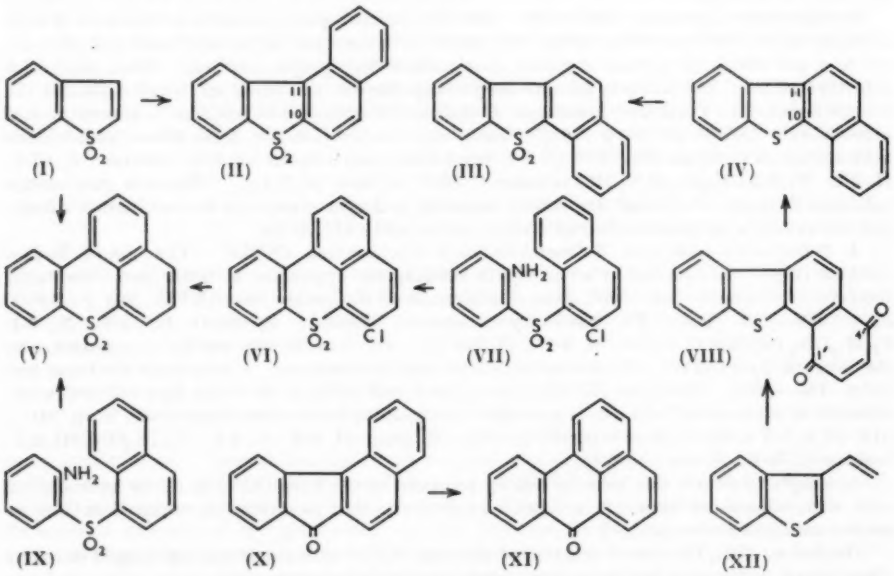
669. *Polymerisation of Thiophen Derivatives. Part VII.* The Conversion of Thionaphthen* 1 : 1-*Dioxide into* 1 : 10-*Benzothiaxanthen* 5 : 5-*Dioxide.*

By W. DAVIES, Q. N. PORTER, and J. R. WILMSHURST.

The product, m. p. 195—196°, formed by heating undiluted thionaphthen 1 : 1-dioxide (I) at 195° and claimed [1] as 9-thia-1 : 2-benzofluorene 9 : 9-dioxide (III), is now found to be the isomeric 1 : 10-benzothiaxanthen 5 : 5-dioxide (V).

BY carrying out the decomposition of thionaphthen 1 : 1-dioxide (I) at 195° on a relatively large scale, it is now found that 9-thia-3 : 4-benzofluorene 9 : 9-dioxide (II) can be isolated, as well as the sulphone, m. p. 195—196°, previously obtained.[1] The latter was also made by a Pschorr reaction on *o*-aminophenyl 1-naphthyl sulphone (IX), and the identity of these two compounds [previously regarded as having structure (III)—contrast below] is now confirmed by ultraviolet absorption spectra.



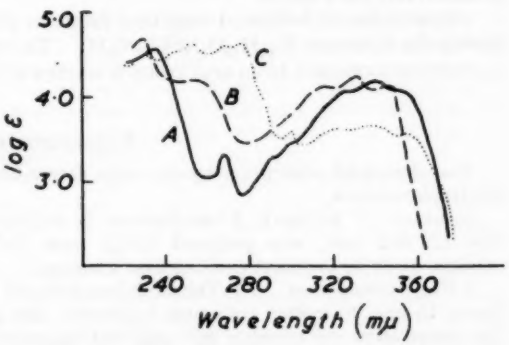
In the course of a new general synthesis of polycyclic thiahydrocarbons which will be described later, the sulphone (III) has been prepared by an unambiguous process and is

* Part VI, *J.*, 1957, 826.

[1] Davies, James, Middleton, and Porter, *J.*, 1955, 1565.

found to have m. p. 236° and not 196°. 3-Vinylthionaphthen (XII) is condensed with benzoquinone and the initial adduct is dehydrogenated by excess of benzoquinone to 1 : 2-benzo-9-thiafluorene-1′ : 4′-quinone (VIII), which is reduced with lithium aluminium hydride to the thiahydrocarbon, m. p. 185—186°. This is the m. p. of 1 : 2-benzo-9-thiafluorene (from coal tar), which was desulphurised to 2-phenylnaphthalene by Kruber and Grigoleit [2] who, however, did not prepare its sulphone. Our synthetic product is readily oxidised with hydrogen peroxide in acetic acid to form 1 : 2-benzo-9-thiafluorene 9 : 9-dioxide (III), m. p. 236°. This is the m. p. of the sulphone from the thiahydrocarbon, m. p. 185—186°, made in a different way [3] and these two compounds (kindly supplied by Professor Badger) are identical (mixed m. p.) with those derived from 3-vinylthionaphthen. The two sulphones, m. p. 196° and 236° respectively, have different solubilities and ultraviolet absorption spectra.

The evidence that the thionaphthen 1 : 1-dioxide pyrolysis product, m. p. 196°, had structure (III) was that of James,[4] who desulphurised it with Raney nickel to a compound accepted as 2-phenylnaphthalene because its m. p. 102—103° was undepressed on admixture with an authentic specimen. This desulphurisation is under investigation, but so far attempts to repeat it have failed.



Ultraviolet absorption of (A) compound (V), (B) benzanthrene, and (C) compound (III) in 95% ethanol.

It therefore seems that in the Pschorr reaction with (IX) cyclisation has occurred in the *peri*-position, and that the product is 1 : 10-benzothiaxanthen 5 : 5-dioxide (V). This was proved by the synthesis of the compound (V) in such a way that only the *peri*-position is available for cyclisation. The Pschorr reaction with *o*-aminophenyl 2-chloro-1-naphthyl sulphone (VII) rapidly gives about a 50% yield of 4-chloro-1 : 10-benzothiaxanthen 5 : 5-dioxide (VI), which has an ultraviolet absorption spectrum similar to that of the dioxide (V). Not only can the chlorine be removed by lithium aluminium hydride to form a small yield of (V), but the reduction can proceed further to form a (slightly impure) thiahydrocarbon which is oxidised in high yield by hydrogen peroxide to give (V), m. p. 196°. The identity of the two products from the sulphones (I) and (VII) is established by the mixed melting points and by identical ultraviolet absorption spectra.

In the cyclisation of *o*-aminophenyl 1-naphthyl sulphone (IX) the yield of pure product is about 33%, and it is apparent that *peri*- and not *ortho*-cyclisation is favoured. The formation of a *peri*-link in the heating of undiluted thionaphthen dioxide (I) is however remarkable, since an 89% yield of 10 : 11-dihydro-9-thia-3 : 4-benzofluorene 9 : 9-dioxide (cf. II) is formed in solution at a slightly lower temperature.[1] In the experiments without solvents the self-condensation of thionaphthen 1 : 1-dioxide with the production of the sulphone (II) and sulphur dioxide, essentially follows a normal course, but production of

[2] Kruber and Grigoleit, *Chem. Ber.*, 1954, **87**, 1895.
[3] Badger and Christie, *J.*, 1956, 3438.
[4] James, Thesis, Melbourne, 1954, p. 115.

the isomer (V) and of 9-thia-3 : 4-benzofluorene is abnormal. It is possible that in the acid environment 9-thia-3 : 4-benzofluorene 9 : 9-dioxide (II) suffers fission and rearranges to (V). A purely formal analogy to this is the conversion [5] of 3 : 4-benzofluorenone (X) into benzanthrone (XI) by aluminium chloride and sodium chloride at 100—150°. However, such rearrangement has not yet been observed with pure 9-thia-3 : 4-benzothiafluorene 9 : 9-dioxide (II) or its 10 : 11-dihydro-derivative.

Reduction of 1 : 10-benzothiaxanthen 5 : 5-dioxide (V) with lithium aluminium hydride gives a crimson solution which on decomposition with water yields a dihydro-derivative. This cannot be 10 : 11-dihydro-9-thia-1 : 2-benzofluorene 9 : 9-dioxide (cf. IV),[1] and this structure should be removed from the literature.[1,6] The dihydro-derivative of the *peri*-compound (V) forms a dibromo-derivative, which is dehydrobrominated with pyridine to regenerate the sulphone (V). The structure of the dihydro-derivative and the implications of the formation of the crimson colour will be further studied. It is remarkable that very brief exposure of the chloro-compound (VI) to lithium aluminium hydride is sufficient to remove the chlorine, and also the oxygen to a considerable extent.

It is noteworthy that the ultraviolet absorption spectrum [7] of benzanthrene, the hydrocarbon derived from (XI), closely resembles that of (V), which is quite unlike that of genuine (III) (cf. Figure).

o-Aminophenyl 2-chloro-1-naphthyl sulphone (VII) separates from benzene in crystals having the structure $(C_{16}H_{12}O_2NSCl)_2,C_6H_6$. The question of steric effects in naphthalene derivatives connected to an aryl group is worthy of further examination.

Experimental

The ultraviolet absorption spectra were determined in 95% EtOH with a Hilger Uvispek spectrophotometer.

Synthesis of 9-Thia-1 : 2-benzofluorene 9 : 9-Dioxide.—2-3′-Thionaphthenylethanol, b. p. 125—128°/0·2 mm., was prepared (75%) from 3-thionaphthenylmagnesium bromide and ethylene oxide by Cagniant and Cagniant's method.[8]

3-Vinylthionaphthen. 2-3′-Thionaphthenylethanol (60 g.) in toluene (60 ml.) was added during 15 min. to molten potassium hydroxide (250 g.) in a distillation flask at 230°/15 mm. The temperature was raised to 260° until distillation ceased. The aqueous layer of the distillate was separated, and the organic layer was concentrated and distilled, giving *3-vinylthionaphthen*, b. p. 133—134°/25 mm. (35·5 g., 66%) (Found : C, 74·6; H, 4·7. $C_{10}H_8S$ requires C, 75·0; H, 5·0%).

Reaction with benzoquinone. 3-Vinylthionaphthen (1·5 g.) and benzoquinone (4·5 g.) in glacial acetic acid (30 ml.) were heated on the water-bath for 8 hr. The product that separated on cooling was washed with ether, and recrystallised from benzene, giving orange-red needles of *9-thia-1 : 2-benzofluorene 1′ : 4′-quinone* (VIII), m. p. 197—198° (2·1 g., 80%) (Found : C, 72·4; H, 3·3. $C_{16}H_8O_2S$ requires C, 72·7; H, 3·0%).

Reduction. The above quinone (1·0 g.) was extracted (Soxhlet) with tetrahydrofuran (50 ml.) containing lithium aluminium hydride (1·0 g.) for 15 hr. The excess of hydride was decomposed with moist ether, and inorganic material dissolved with hydrochloric acid. The organic layer on concentration gave 9-thia-1 : 2-benzofluorene (IV), m. p. 185—186° (0·7 g.), undepressed on admixture with a genuine sample [3] (Found : C, 82·3; H, 4·5. Calc. for $C_{16}H_{10}S$: C, 82·05; H, 4·3%).

Oxidation. The above thiahydrocarbon (0·25 g.) was heated on the water-bath for 1 hr. with 30% hydrogen peroxide (0·75 ml.) and acetic acid (1·5 ml.). The product that separated on cooling was crystallised from ethanol, giving needles of 9-thia-1 : 2-benzofluorene 9 : 9-dioxide [3] (III), m. p. and mixed m. p. 235·5—236° (Found : C, 72·2; H, 3·9. Calc. for $C_{16}H_{10}O_2S$: C, 72·2; H, 3·8%).

[5] Baddar, *J.*, 1941, 310.
[6] Davies and Porter, *J.*, 1957, 827.
[7] Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," Chapman-Hall, London, 1951, Fig. 436.
[8] Cagniant and Cagniant, *Bull. Soc. chim. France*, 1949, 382.

Action of Heat on Thionaphthen Dioxide (I).—The heating of the dry dioxide (10 g.) at 195° for 25 min. was essentially as previously described.[1] Some water was formed, and the crude dark-green solution in benzene was chromatographed on alumina. The eluate from the first band (yellow, yellow fluorescence in ultraviolet light) gave an oil (5·4 g.), which with hydrogen peroxide gave the sulphone (II), m. p. 234° (0·55 g.), indicating the presence of about 0·5 g. of 9-thia-3 : 4-benzofluorene, which is itself isolated with difficulty. The second band, colourless, but fluorescing pale-blue in ultraviolet light, on arbitary fractionation, gave 0·5 g. of the above sulphone (II), and also crystals (0·4 g.), m. p. 196°. This is identical (mixed m. p.) with the specimen previously prepared,[1] and also with the Pschorr product (mixed m. p. and ultraviolet absorption) from *o*-aminophenyl 1-phenylnaphthalene sulphone (IX). Attempts were made to desulphurise the sulphone, m. p. 196° (from I), by the method previously described. With one specimen of Raney nickel part of the sulphone was recovered, and with a more reactive nickel all the sulphone (0·2 g.) was apparently reduced but the oil (about 0·01 g.) could not be identified. The reduction with Raney nickel of this and allied sulphones is being investigated.

Synthesis of 4-*Chloro*-1 : 10-*benzothiaxanthen* 5 : 5-*Dioxide* (VI).—An aqueous solution (200 ml.) containing sodium 2-aminonaphthalene-1-sulphonate (50 g.) and sodium nitrite (18 g.) was rapidly added to concentrated hydrochloric acid (150 g.) and ice (150 g.), and the process of Dikshit and Tilak[9] then followed, to give a good yield of sodium 2-chloronaphthalene-1-sulphonate and thence (by phosphorus pentachloride) 2-chloronaphthalene-1-sulphonyl chloride. Into a suspension of stannous chloride dihydrate (250 g.) in acetic acid (600 ml.) dry hydrogen chloride was passed until the salt dissolved; 2-chloronaphthalene-1-sulphonyl chloride (30 g.) was then added. After 18 hr. at room temperature, addition of concentrated hydrochloric acid precipitated 2-chloronaphthalene-1-thiol, m. p. 65—65·5°.

2-*Chloro*-1-*naphthyl* o-*nitrophenyl sulphide*, yellow prisms, m. p. 141—142° (from ethanol), was obtained (15 g.) by refluxing 2-chloronaphthalene-1-thiol (10 g.) and *o*-chloronitrobenzene (10 g.) in ethanol (30 ml.) with 30% aqueous sodium hydroxide (30 ml.) for 1 hr. (Found : C, 60·8; H, 3·3; N, 4·2. $C_{16}H_{10}O_2NSCl$ requires C, 60·9; H, 3·2; N, 4·4%).

2-*Chloro*-1-*naphthyl* o-*nitrophenyl sulphone*, very pale-yellow needles, m. p. 145·5—146° (from ethanol), was prepared (9·3 g.) by refluxing for 1 hr. the above sulphide (10 g.) in acetic acid (100 ml.) containing 30% hydrogen peroxide (15 ml.) (Found : C, 55·6; H, 3·0. $C_{16}H_{10}O_4NSCl$ requires C, 55·3; H, 2·9%).

o-*Aminophenyl* 2-*chloro*-1-*naphthyl sulphone* (VII), plates, m. p. 193—194° (from ethanol), was isolated (1·4 g.) by making alkaline a solution of the above nitro-sulphone (2 g.) which had been refluxed for 1 hr. in acetic acid (40 ml.) containing stannous chloride hydrate (15 g.) and concentrated hydrochloric acid (10 ml.) (Found : C, 60·6; H, 4·05. $C_{16}H_{12}O_2NSCl$ requires C, 60·5; H, 3·8%). The crystals from benzene crumble when heated, and the analyses of different samples indicate that benzene of crystallisation is firmly held, about 30% being lost at 60°/20 mm. in 3 hr. However, 11·572 mg. of air-dried crystals [Found : C, 63·8; H, 4·3. $(C_{16}H_{12}O_2NSCl)_2,C_6H_6$ requires C, 64·0; H, 4·2%], from benzene, in a stream of oxygen for 20 min. at 150—160° gave (by difference) 1·312 mg. of volatile material (Found : C, 92·4; H, 7·9. Calc. for C_6H_6 : C, 92·3; H, 7·7%) and 10·260 mg. of a colourless non-volatile residue (Found : C, 60·6; H, 3·8%. Calc. as for the above specimen from ethanol). This result corresponds to 1·04 moles of benzene per two moles of sulphone.

Pschorr Reaction with o-*Aminophenyl* 2-*Chloro*-1-*naphthyl Sulphone*.—This amine (1 g.) in acetic acid (20 ml.) and concentrated hydrochloric acid (20 ml.) was diazotised at 8° with sodium nitrite (0·28 g.) in water (2 ml.). Urea (1 g.) was added after 1 hr. at room temperature, then after 5 min. freshly prepared copper powder (1 g.), a vigorous reaction ensuing. After an hour the mixture was diluted with water, precipitating an additional amount of 4-*chloro*-1 : 10-*benzothiaxanthen* 5 : 5-*dioxide* (VI) (0·45 g.), needles, m. p. 205·5—206° (from ethanol) (Found : C, 63·7; H, 3·05. $C_{16}H_9O_2SCl$ requires C, 63·9; H, 3·0%).

Conversion of 4-*Chloro*-1 : 10-*benzothiaxanthen* 5 : 5-*Dioxide into* 1 : 10-*Benzothiaxanthen* 5 : 5-*Dioxide* (V).—4-Chloro-1 : 10-benzothiaxanthen 5 : 5-dioxide (0·4 g.) in benzene (30 ml.) and ether (100 ml.) was refluxed with lithium aluminium hydride (0·2 g.), and the solution rapidly became crimson. This colour persisted until (45 min.) water was added. The organic solution was washed with dilute sulphuric acid, dried ($MgSO_4$), and yielded an oil which was extracted with light petroleum (30 ml.; b. p. 60—80°). The petroleum-insoluble residue was chromatographed in benzene on alumina, and the blue fluorescent (ultraviolet light) band

[9] Dikshit and Tilak, *Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 78.

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yielded crystals (8 mg.), m. p. 195—196°. This compound is identical (mixed m. p.) with the compound of the same m. p. made by the Pschorr reaction on *o*-aminophenyl 2-naphthyl sulphone.[1] The ultraviolet absorption spectra were identical.

The light petroleum-soluble material was similarly chromatographed and yielded a yellow waxy solid, with blue fluorescence in ultraviolet light, m. p. 50—60°. It (0·08 g.) in benzene (2 ml.) when added to 2 : 4 : 7-trinitrofluorenone (0·1 g.) in hot benzene–alcohol (30 ml.; 1 : 1) gave the slightly impure *addition compound*, black needles with a black smear, m. p. 221—222° (0·14 g.) (from benzene–ethanol) (Found: C, 62·7; H, 2·7; N, 7·0. $C_{29}H_{15}O_7N_3S$ requires C, 63·4; H, 2·75; N, 7·65%). This compound (0·1 g.), in benzene (20 ml.), was decomposed by chromatography through a short column of alumina, and the 1 : 10-*benzo-5-thiaxanthen* (0·04 g.), yellow needles, m. p. 79—80° (from ethanol), gave a benzene solution with blue fluorescence in ultraviolet light (Found: C, 81·1; H, 4·3. $C_{16}H_{10}S$ requires C, 82·0; H, 4·3%).

This thiahydrocarbon (0·05 g.) in acetic acid (2 ml.) was refluxed for an hour with excess of hydrogen peroxide, and yielded (0·04 g.) 1 : 10-benzothiaxanthen 5 : 5-dioxide, m. p. 196° (from ethanol). It was identical (mixed m. p. and identical ultraviolet absorption spectra) with the product, m. p. 196°, from the Pschorr reaction (Found: C, 72·1; H, 3·94. Calc. for $C_{16}H_{10}O_2S$: C, 72·2; H, 3·8%).

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UNIVERSITY OF MELBOURNE, AUSTRALIA. [*Received, March 13th*, 1957.]

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670. *Anodic Processes. Part IV.* The Anodic Generation of Calomel.*

By H. P. DIBBS, D. J. G. IVES, and R. W. PITTMAN.

The initial stages of the anodic generation of calomel at the interface between mercury and dilute aqueous hydrochloric acid have been further examined in galvanostatic experiments, with oscillographic recording of the dependence of potential upon time. The influence of acid concentration and of temperature has been studied. Assessments of the current efficiency of calomel production, and the examination of open-circuit potential decay curves have been used to support and extend earlier interpretations of the interfacial phenomena which occur.

IT has been shown [1,2,3] that anodisation of mercury in dilute, aqueous hydrochloric acid is accompanied by a complex sequence of phenomena terminating in the formation of a passivating film of uniquely oriented, crystalline calomel.[4] It was of particular interest that oscillographic records of electrode potential at constant current density showed a number of transient singularities which marked a dramatic transition between polarised and reversible states. The present paper records further observations on these phenomena, with particular reference to their dependence on temperature and acid concentration. Experiments are also recorded which make some progress towards the elucidation of the electrode processes.

The characteristics of the oscillograms taken under galvanostatic conditions [5] may be recalled by reference to Fig. 1, which illustrates the effects of temperature at constant current density and acid concentration. It will be seen that a low temperature favours the full development of " fine structure," the features *a*, *b*, *c*, and *d*, previously assigned the trivial names " prepeak," " peak," " minimum," and " hump," being clearly visible.

* Part III, *J.*, 1953, 3988.

[1] Cousens, Ives, and Pittman, *J.*, 1953, 3972.
[2] *Idem, ibid.*, p. 3980.
[3] *Idem, ibid.*, p. 3988.
[4] Thirsk, *Proc. Phys. Soc.*, 1953, **66**, *B*, 129.
[5] Gerischer, *Z. Elektrochem.*, 1955, **59**, 604.

The parameters of the points *a*, *b*, and *c* are reproducible within experimental error. They are characterised, for example, by overpotentials (referred to the appropriate calomel potential) which, for 0·1N-hydrochloric acid at 25°, fall upon Tafel lines with slopes of 3·2, 5·6, and 3·5 mv. The quantity of electricity required for the transition between *a* and *c* is always of the order of 90 μc cm.$^{-2}$, independently of acid concentration, temperature, and current density, as long as the " fine structure " remains undegraded.

It is evident from Fig. 1 that rising temperature smooths out the potential changes : there is a progressive degradation, with loss of fine structure. This effect is general, and

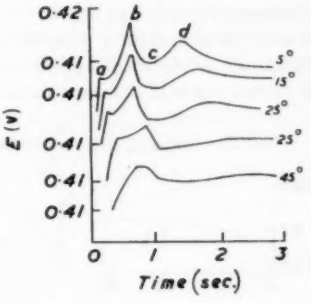
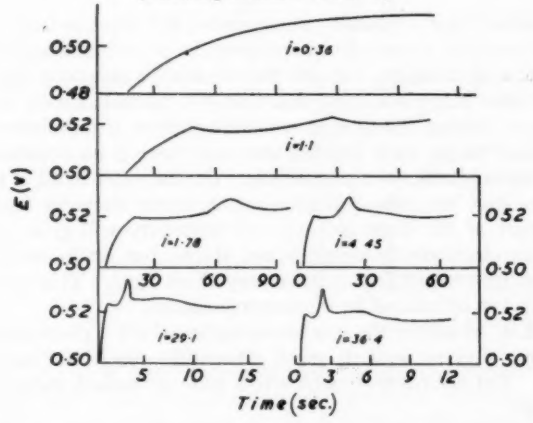


FIG. 1. *Potential–time curves for different temperatures and* 0·01N-HCl *at current density* (*i*) 91·8 μA *cm.*$^{-2}$. (*Calomel potential* = 0·391 v *at* 25°.)

FIG. 2. *Potential–time curves for different current densities* (*i*, *in* μA *cm.*$^{-2}$) *in* 0·01N-HCl. (*Calomel potential* = 0·511 v.)



can lead ultimately to loss of all special characteristics, leaving only a smoothly rising curve, very similar to those which are obtained with anodisations at very low current densities. It is noteworthy, however, that, when in a particular case this degradation has been brought about by rise in temperature, it can be reversed by an increase in current density.

The temperature effect can be described in more detail. Thus, the temperature coefficients of the points *a*, *b*, *c*, and *d*, for the conditions appertaining to Fig. 1, have the values, constant over the temperature range 5—45°, of 0·19, −0·09, 0·09, and 0·00 mv deg.$^{-1}$, figures which can be related, by inspection, to the changing shapes of the curves.

The influence of acid concentration has been studied in experiments at the additional concentrations of 0·01N and 1N. At the lower concentration, it has been found that there is an enhanced tendency for the fine structure of the potential–time record to develop; it

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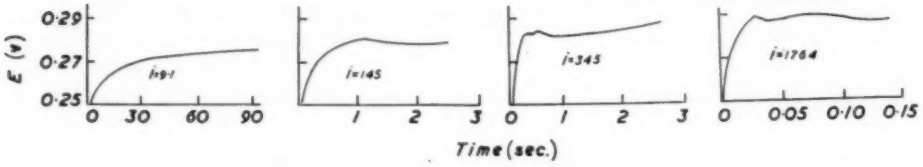
appears at a lower current density than for the 0·1N-acid, but is equally vulnerable to rise of temperature. The growth of the fine structure with increasing current density at a constant temperature of 25° is illustrated in Fig. 2, which is closely similar, except for the scale of current density, to Fig. 1 (relating to 0·1N-acid) in Part II.[2] However, the Tafel slopes relating to the potentials of the points *a*, *b*, and *c* had the somewhat higher values of 4·4, 8·4, and 5·0 mV for the more dilute solution.

For the higher acid concentration (N), the reverse tendency was outstanding; the oscillograms showed almost complete absence of fine structure, except at the lowest temperatures and relatively high current densities. This is illustrated in the sequence of oscillograms recorded in Fig. 3.

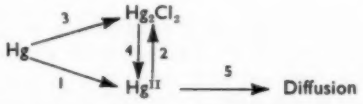
From these results a general conclusion may be drawn that the fine structure of the oscillograms tends to disappear with falling current density, with rising temperature, or with increasing acid concentration. An explanation of these trends is readily accessible.

FIG. 3. *Potential–time curves for different current densities* (*i*, *in* μA *cm.*$^{-2}$) *in* N-HCl *at* 5°.



It may be recalled [1] that a quantity of electricity 10^9 times as large as that required to saturate the whole solution phase with calomel can be passed anodically across a mercury–dilute hydrochloric acid interface without the electrode's attaining the calomel potential or achieving reversible behaviour, provided that the current density is low and that the potential–time curve during the flow of constant current is uninflected. Mercuric compounds are generated during such anodisations, and there is no evidence for the existence of calomel as an intermediate, even transiently. On the other hand, if the current density is high enough to give an inflected polarisation curve showing features *a*, *b*, and *c*, one thousandth part of the same quantity of electricity will give a reversible calomel electrode. Such an electrode, however, is not stable, but drifts away from the calomel potential and loses its reversibility after a very short time. This spontaneous decay is undoubtedly due to loss of calomel by disproportionation.

It is obvious that, whatever the conditions under which a given degree of oxidation is effected anodically, a given system must ultimately reach the same thermodynamic equilibrium state. But the route by which this state is reached varies in accordance with the reaction scheme :



where the sequence, 1, 2, occurs exclusively at very low current densities, giving place to 3, 4 at higher ones, the transition occurring suddenly. That reactions 1 and 4 should be favoured by rise in temperature, and by increase in hydrochloric acid concentration, is to be expected, and explains all of the recorded trends.

Experiments have been made to assess the current efficiency of calomel production under various conditions, and thus to trace the changing balance between the initial steps 1 and 3, as far as they can be isolated from the succeeding reactions, by passing a fixed charge, q_a, anodically at constant current density, followed by an immediate cathodic reduction at the same current density, until the electrode potential " slipped " suddenly

from its steady value close to the calomel potential. The charge passed cathodically, q_c, could then be regarded as approximately proportional to the quantity of calomel produced at the electrode surface in the preceding anodisation. Values of q_c/q_a, as a function of current density, for four temperatures and three acid concentrations, are represented graphically in Fig. 4.

All the curves are consistent with zero current efficiency of calomel production as the current density is indefinitely decreased. The very sharp rise of this quantity over a narrow range of current densities in some cases is evident, this being most marked when temperature and acid concentration are low. The rise also coincides with the transition from a featureless anodic polarisation curve to one which shows fine structure. The very great fall in yield of calomel at the highest acid concentration reflects the rapidity of the disproportionation, 4, under these conditions, as well as the greater facility of reaction 1.

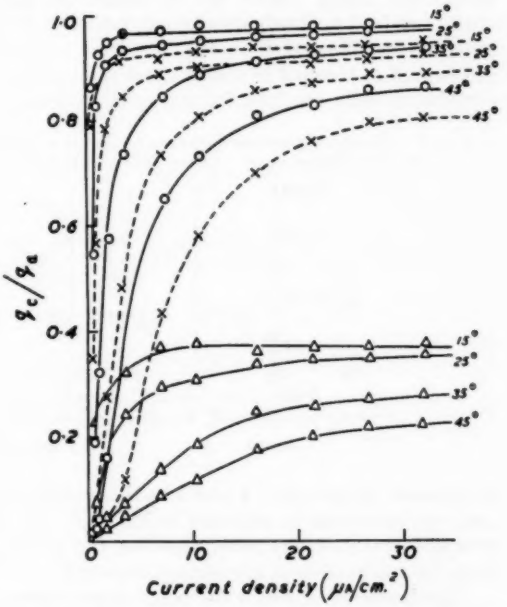


FIG. 4. *Plots of q_c/q_a as a function of current density (i, in μA cm.$^{-2}$). (q_a = 1820 μC cm.$^{-2}$.)*

Normality of HCl:
○, 0·01; ×, 0·1; △, 1·0.

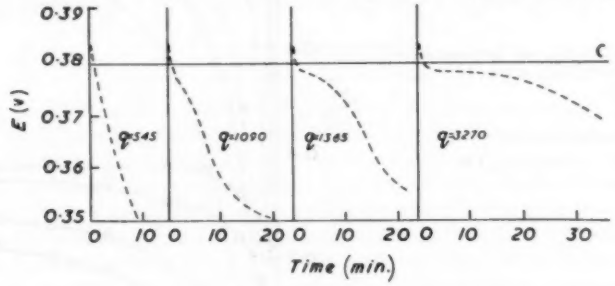
Although all the curves of Fig. 4 are affected by the continuous loss of calomel by disproportionation, both during anodisation and cathodic reduction, it is clear that a fairly comprehensive picture has been obtained of how the suggested reaction scheme responds to changing conditions. Of the two competing reaction paths, that involving calomel production (3, 4) is of immediate interest.

The states through which an electrode passes from the instant at which anodic polarisation is started are reflected in the fine structure of the potential records, and are difficult to examine because of their transience. The method previously used,[2] of arresting anodisation at various stages and studying the course of subsequent open-circuit potential changes has, however, been exploited with some success. It has been confirmed that the occurrence of fine structure, including *a*, *b*, and *c* (cf. Fig. 1), in the anodic polarisation curve is essential for the appearance of a well-defined arrest at the calomel potential in the post-anodisation potential decay curve. The length of the arrest increased proportionally with the time, for a given current density, that anodisation is continued after the point *c* has been traversed; that is, after the peak has been surmounted. If, on the other hand, for a similar anodic charge, conditions of temperature, concentration, and current density

are such that the anodic polarisation curve is smoothly rising, the subsequent decay curve shows no arrest or inflection, except as now discussed. This procedure can clearly distinguish between the two alternative paths of the reaction scheme, 1 or 3, 4, but to either of these should be added a step, 5, indicating the diffusion of soluble oxidation products away from the interface into the bulk of the solution. In general, the results of a large number of these " decay experiments " confirm all the conclusions, reached by other means, about the effect of the three independent variables upon electrode behaviour, and leave no doubt that the processes responsible for " the peak " are intimately associated with the appearance of calomel as a stable, potential-determining phase. It has been possible, however, to explore the fine structure of the anodic polarisation curves in greater detail than this, with the following results.

Although polarisations at low current density, with smooth potential changes, give uninflected decay curves for moderate charges, protracted anodisations under these conditions lead to slowly developing, rather ill-defined arrests somewhat below the calomel potential, as illustrated in Fig. 5. It is suggested that these represent the secondary production of calomel in the reaction sequence 1, 2. Since the interfacial zone is not in equilibrium with the bulk solution phase during, and shortly after, anodisation, this will

FIG. 5. *Change of potential with time for different anodic charges (q, in μC cm.⁻²), in 0·01N-HCl at 35° and 0·91 μA cm.⁻². (The line C here and in Figs. 6—7 denotes the calomel potential.)*



be followed by processes 4 and 5 as this equilibrium is established. This is in conformity with the observations reported in Part I,[1] and with the knowledge that a satisfactorily reversible calomel electrode, showing the proper thermodynamic potential, cannot be made by anodisation at low current density.[6]

Anodisations, of which the polarisation curves showed fine structure, were carried out with fixed, pre-determined charges at gradually increasing current densities. It is of interest that in this way a sequence of oscillograms was obtained showing abrupt termination at stages advancing in the sequence *a*, *b*, *c* (cf. Fig. 1) along the complex polarisation curve, confirming that, over quite a narrow range of current density, reaction 1 supplants reaction 3 in predominance. It has been found that the crossing of the prepeak, *a*, marks the appearance of inflections in the decay curve, but it is of great interest that if the prepeak *alone* is crossed, there are two inflections, one above the calomel potential, and one below it, with none at the calomel potential itself. As the point of termination of the anodisation moves along the " saddle " between the prepeak and the peak (*a* to *b*), the lower inflection becomes more marked and rises towards the calomel potential. This was noted in the earlier work,[2] in which, unfortunately, the upper inflection was missed. The attainment of the crest of the peak, *b*, marks the first appearance of an arrest at the calomel potential itself, and this arrest becomes more clear-cut and prolonged the longer the anodisation is continued beyond this point. The impression has been gained that traverse of the point *c* is marked by a " cleaner " and more rapid decay from the calomel potential.

[6] Hills and Ives, *J.*, 1951, 311.

These statements are based upon the results of a large number of experiments. The maximum speed of manual manipulation set a rather low limit to the current density which could be used. This gave a less clear-cut separation between reactions 1 and 3 than

FIG. 6. *Change of potential with time at different current densities (i, in μA cm.⁻²) for 0·01N-HCl at 15° and 73 μC cm.⁻².*

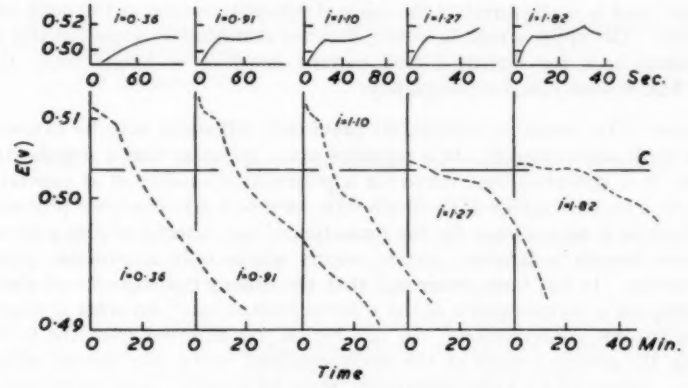


FIG. 7. *Change of potential with time at different current densities (i, in μA cm.⁻²) for 0·01N-HCl at 15° and 36·5 μC cm.⁻².*

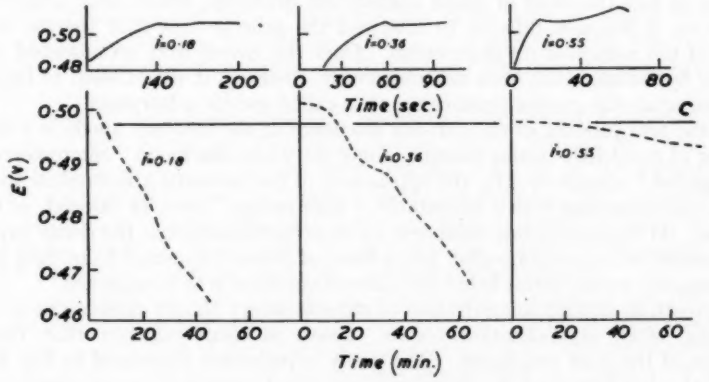
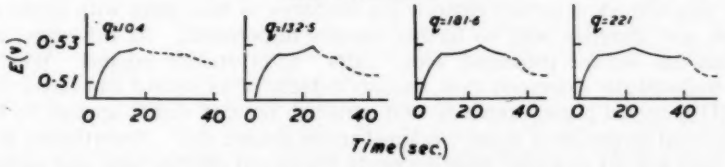


FIG. 8. *Change of potential with time for different anodic charges (q, in μC cm.⁻²) for 0·01N-HCl at 35° and 5·64 μA cm.⁻².*



could have been desired, and less than the maximum development of fine structure in the anodic polarisation curves. Typical results are illustrated in Figs. 6—8.

In the experiment recorded in Fig. 8, the alternative procedure of passing increasing anodic charges at a fixed current density was used, the early stages of potential decay being

recorded on the same oscillograph sweep as the polarisation curve. The course of the open-circuit potential is, in each case, shown by a broken line. It is of interest that no immediate fall of potential is discernible when the current-carrying circuit is broken; there is little or no overpotential. This stands in marked contrast to the polarisations at very low current density involving reaction 1 alone, where there is a considerable overpotential (cf. Part I [1]). The arrest in potential decay above the calomel potential is clearly visible, and so is the arrest at the calomel potential as soon as the peak summit has been attained. The upper arrest, however, does not immediately vanish at this stage, but rapidly declines and, for slightly higher current densities or longer times than those recorded in Fig. 8, soon vanishes completely.

Discussion.—The tentative conclusions previously advanced may be extended in the light of the work now reported. It is regarded as an aphorism that a singularity, such as the prepeak, in a potential–time curve for a polarisation conducted at constant current density marks a sudden change in electrode state, or a switch in electrode process. Before the prepeak there is no evidence for the formation of any interfacial film and no trace of calomel, even though a faradaic process occurs whose only identifiable products are mercuric entities. It has been confirmed that the differential capacity of the electrode before the prepeak is surmounted is of the order of 1000 μF cm.$^{-2}$, an order of magnitude for which there is some confirmation.[7] In this region, far removed from the point of zero charge along the anodic branch of the electrocapillary curve, the specific adsorption of chloride ions, reinforced by Volta adsorption, must be intense. Yet the evidence is clear that no direct chloride-ion discharge occurs until the prepeak is passed, after which the evidence for it is insurmountable. It is believed that the switch of electrode process at the prepeak is in fact the onset of direct chloride-ion discharge, where none occurred before. If this is so, it becomes difficult to interpret the general view that specific adsorption partakes of the nature of covalent union. Once the switch from an adsorbed state to a covalently bound state has been unambiguously observed, it would seem to be necessary to examine again the precise significance of so-called specific adsorption.

That the first product of chloride-ion discharge at the mercury anode is a disordered monolayer of covalently bound chlorine atoms, for which the name " chloromercury " has been suggested,[6] is supported by the appearance of the potential arrests *above* the calomel potential, corresponding with a metastable, " high-energy " form of calomel, or precursor to calomel. If the loss of this substance by disproportionation in the decay experiments is accompanied by a transformation into a trace of calomel too small to be fully potential-determining, the second arrest below the calomel potential is to be expected.

The growth in surface concentration of chloromercury should cause a rise in potential terminating when crystallisation occurs. There is clear evidence that this is the significance of the peak maximum. The decay experiments illustrated in Fig. 8 indicate that once this has happened the disordered interfacial " phase " rapidly disappears. The crystallisation, taking place in response to " intermolecular " attractions, is no doubt accompanied by a contraction, generating free space on the formerly over-populated surface; this will allow further chloride-ion discharge to take place with relatively little hindrance, and therefore with no further increase of potential. At this stage, however, the surface has become populated with " rafts " of crystalline calomel. Whether this calomel, undoubtedly extremely thin, consists initially of an *ordered* monolayer (in effect, a single {110} crystal plane) cannot be said, although the fact that it appears to have the electrochemical properties of massive calomel argues against this. Nevertheless, it is likely that the rafts will act as nuclei, building newly discharged chloride ions, and mercury ions from the substrate, into their lattices. Lateral growth of the thin islets will be favoured, and a point may be reached when the free surface again becomes restricted. If the rate of chloride-ions discharge, defined by the current density, is great enough, this may lead to

[7] Rosental and Ershler, *J. Phys. Chem. U.S.S.R.*, 1948, **22**, 1344.

a significant hindrance which may be the basis of the hump, *d*, the least well-defined feature of the fine structure. Relief from this state is attributed to a recrystallisation process, which will be shown in Part V to play an essential rôle in the later stages of the anodisation process.

The experimental methods used in the present work were similar to those previously employed.[2]

One of us (H. P. D.) thanks the Durham Education Authority and Messrs. Albright and Wilson Ltd. for maintenance grants.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, March 18th*, 1957.]

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671. *The Alkaline Hydrolysis of Glucose Nitrates.*

By D. O'MEARA and D. M. SHEPHERD.

The alkaline hydrolysis of a series of mono-, di-, and tri-nitrates of methyl β-D-glucoside has been studied. The results can be interpreted in terms of the currently accepted mechanisms of nitrate hydrolysis.

BAKER and EASTY [1] and Cristol, Franzus, and Shadan [2] have shown that three types of reaction are involved in the alkaline hydrolysis of nitrate esters, *viz.*, nucleophilic substitution (S_N2), β-hydrogen elimination ($E2$), and α-hydrogen elimination (E_{CO}). The last reaction yields a carbonyl compound and inorganic nitrite, while in the other reactions nitrate is the only inorganic product. Thus, the amount of nitrite released is a measure of the extent of the E_{CO} reaction.

The work of Gladding and Purves [3] suggests that, in the alkaline hydrolysis of certain glucose mononitrates, the E_{CO} reaction occurs to only a slight extent, the S_N2 reaction predominating. Later studies by Ansell and Honeyman [4] and by Honeyman and Morgan [5] support this view.

With glucoside 2 : 3-dinitrates, however, Honeyman and Morgan [5] observed considerable degradation with liberation of inorganic nitrite, and in the case of methyl **4 : 6-*O*-**benzylidene-α-D-glucoside 2 : 3-dinitrate they obtained evidence of the formation of an α-diketone. Their results indicate that the nitrate groups on $C_{(2)}$ and $C_{(3)}$ are eliminated largely by the E_{CO} mechanism, although, from the products isolated, it is clear that the S_N2 reaction also occurs to some extent. In the hydrolysis of alkyl D-glucoside **2 : 3 : 4 : 6-**tetranitrates Shepherd [6] has shown that the E_{CO} reaction predominates.

Thus it is evident that various factors, *e.g.*, the degree of nitration and the nature of other substituents, affect the extent of the E_{CO} reaction in the alkaline hydrolysis of glucose nitrates, and in view of the supposed pharmacological significance of nitrite release associated with such hydrolysis, the experiments summarised in Tables 1—5 have now been carried out.

The results show that with mononitrates the amount of nitrite released is relatively small, but as the number of nitrate groups is increased (Tables 2—5), there is a very marked increase in the extent of the E_{CO} reaction. Substitution of free hydroxyl by ethylidene groups (Tables 1 and 2) or methyl groups (Table 2) increases the extent of the E_{CO} reaction, especially with methyl β-D-glucoside 2 : 3-dinitrate.

The results in Tables 1, 2, and 3 indicate that, in the hydrolysis of acetates of these mono- and di-nitrates, the acetate groups are removed before the nitrate groups, since considerable amounts of alkali are consumed before any inorganic nitrite appears in the

[1] Baker and Easty, *J.*, 1952, 1193.
[2] Cristol, Franzus, and Shadan, *J. Amer. Chem. Soc.*, 1955, **77**, 2512.
[3] Gladding and Purves, *ibid.*, 1944, **66**, 76.
[4] Ansell and Honeyman, *J.*, 1952, 2778.
[5] Honeyman and Morgan, *J.*, 1955, 3660.
[6] Shepherd, *J.*, 1953, 3635.

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reaction mixture; this is not surprising in view of the widespread application of the Zemplén technique for the preferential deacetylation of sugar acetate nitrates. With monoacetate trinitrates (Tables 4 and 5) the removal of acetate and nitrate groups does not occur in controlled stages, this being consistent with Bell and Synge's failure to obtain

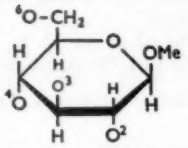

TABLE 1. *Hydrolysis of methyl* β-D-*glucoside mononitrates.*

Substituents						NaOH used	NO_3^- formed
2	3	4	6	Conditions		(Equivs. per mole of ester)	
H	NO_2	H	H	15°,	1 hr.	0	—
				,,	2 hr.	0	—
				B. p.,	2 hr.	0·95	$3·7 \times 10^{-3}$
				,,	,,	0·97	$4·4 \times 10^{-3}$ [a]
Ac	NO_2	Ac	Ac	15°,	1 hr.	2·17	—
				,,	2 hr.	2·17	—
				,,	5 hr.	3·01	—
				,,	7 hr.	3·50	8×10^{-5}
				,,	32 hr.	—	3×10^{-3}
				B. p.,	2 hr.	4·00	$4·3 \times 10^{-3}$
Ac	NO_2	Acx [b]	Ac	15°	1 hr.	1·65	—
				,,	4 hr.	3·03	$2·0 \times 10^{-3}$
				B. p.,	2 hr.	4·03	$5·7 \times 10^{-3}$
H	NO_2	–CHMe–		15°,	1 hr.	0	—
				,,	2 hr.	0	$1·6 \times 10^{-3}$
				B. p.,	2 hr.	0·81	$9·8 \times 10^{-2}$
Ac	NO_2	–CHMe–		15°,	1 hr.	0·56	—
				,,	2 hr.	0·72	$1·6 \times 10^{-3}$
				B. p.,	2 hr.	1·86	$8·0 \times 10^{-3}$
Ac	Ac	NO_2	Ac	15°,	1 hr.	1·80	—
				,,	2 hr.	2·00	—
				,,	28 hr.	—	$9·9 \times 10^{-3}$

[a] 0·26 equiv. of NO_3^- formed. [b] Acx = 1-acetoxyethyl.

TABLE 2. *Hydrolysis of methyl* β-D-*glucoside* 2 : 3-*dinitrate and its derivatives.*

Substituents						NaOH used	NO_3^- formed
2	3	4	6	Conditions		(Equivs. per mole of ester)	
NO_2	NO_2 (m. p. 99—100°)	H	H	15°,	1 hr.	0	—
				,,	2 hr.	0	$3·0 \times 10^{-3}$
				B. p.,	2 hr.	2·50	0·89
NO_2	NO_2 (m. p. 106—107°) [a]	H	H	15°,	1 hr.	0	—
				,,	2 hr.	0	$3·1 \times 10^{-3}$
				B. p.,	2 hr.	2·80	0·92 ff
NO_2	NO_2	Ac	Ac	15°,	1 hr.	0·70	$4·3 \times 10^{-2}$
				,,	2 hr.	1·80	$6·3 \times 10^{-3}$
				B. p.,	2 hr.	4·56	0·95
NO_2	NO_2	Acx [b]	Ac	15°,	1 hr.	1·37	$4·7 \times 10^{-2}$
				,,	2 hr.	1·82	$5·0 \times 10^{-2}$
NO_2	NO_2	Me	Me	15°,	1 hr.	0·26	0·21
				,,	2 hr.	0·30	0·32
				,,	12 hr.	—	0·80
				,,	24 hr.	—	1·18
				,,	36 hr.	—	1·42
				,,	60 hr.	2·00	1·60
NO_2	NO_2	–CHMe–		15°,	1 hr.	0·47	0·36
				,,	2 hr.	0·73	0·43
				,,	4 hr.	0·94	0·61
				22°,	2 hr.	1·00	0·9 [c]
				B. p.,	2 hr.	2·74	1·66

[a] O'Meara and Shepherd.[8] [b] Acx = 1-acetoxyethyl. [c] 40% of starting material recovered.

preferential deacetylation of methyl 6-*O*-acetyl-β-D-glucoside 2 : 3 : 4-trinitrate; [7] indeed the results in Table 4 show that this compound undergoes preferential denitration rather than deacetylation. In the case of methyl 2-*O*-acetyl-β-D-glucoside 3 : 4 : 6-trinitrate, however, the hydrolysis is relatively slow, and it is possible by careful control of the conditions to obtain preferential deacetylation to methyl β-D-glucoside 3 : 4 : 6-trinitrate.[8]

If, in the hydrolysis of methyl 4 : 6-*O*-ethylidene-β-D-glucoside 2 : 3-dinitrate, the reaction is interrupted at the stage where one equivalent of alkali has been consumed and one equivalent of inorganic nitrite liberated, approximately half of the original dinitrate can be recovered unchanged. Clearly, under the conditions used here, selective denitration of the 2 : 3-dinitrate to the 3-nitrate does not occur to any great extent, and it is possible that an α-diketone is one of the primary products of hydrolysis as Honeyman and Morgan [5] have already shown in the case of methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-dinitrate.

In interpreting these results it is helpful to consider the compounds in Table 1 (with the exception of the 4-nitrate triacetate) and in Tables 2 and 4 as derivatives of methyl β-D-glucoside 3-nitrate. In these compounds the introduction of electron-attracting

TABLE 3. *Hydrolysis of methyl* 2 : 3-*di*-O-*acetyl*-β-D-*glucoside* 4 : 6-*dinitrate.*

Conditions	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)	Conditions	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)
15°, 1 hr.	0·96	—	B. p., 2 hr.	3·15	0·12
,, 2 hr.	1·48	—	,, 4 hr.	3·45	0·44
,, 3 hr.	—	$4·67 \times 10^{-3}$			

TABLE 4. *Hydrolysis of methyl* 6-O-*acetyl*-β-D-*glucoside* 2 : 3 : 4-*trinitrate.*

Conditions	NaOH added (Equivs. per mole of ester)	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)	Conditions	NaOH added (Equivs. per mole of ester)	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)
15°, 45 min.	0·96	0·96	0·90 [a]	15°, 45 min.	3·98	3·98	2·41
,, ,,	2·01	2·01	1·42	,, 1 hr.	excess	4·20	2·90
,, ,,	2·97	2·97	1·92	B. p., 2 hr.	,,	4·18	2·70

[a] 20% of starting material unchanged.

TABLE 5. *Hydrolysis of methyl* 2-O-*acetyl*-β-D-*glucoside* 3 : 4 : 6-*trinitrate.*

Conditions	NaOH added (Equivs. per mole of ester)	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)	Conditions	NaOH added (Equivs. per mole of ester)	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)
15°, 1 hr.	1·0	0·58	—	15°, 1 hr.	Excess	1·27	0·59
,, 2 hr.	1·0	0·60	0·37	,, 2 hr.	,,	1·53	0·67
,, 1 hr.	2·0	0·68	0·43	B. p., 2 hr.	,,	4·80	1·20
,, 2 hr.	2·0	0·86	0·46				
,, 1 hr.	3·0	0·80	0·45				
,, 2 hr.	3·0	1·16	0·53				

substituents (*e.g.*, alkoxy or nitrate) into the 2- or 4-position increases the extent of the E_{CO} reaction by facilitating α-hydrogen elimination at $C_{(3)}$. Further, as pointed out by Baker and Easty [9] for nitrates such as ethylene glycol dinitrate in which the nitrate groups are attached to adjacent carbon atoms, a carbonyl group formed on removal of one nitrate group during alkaline hydrolysis, being electron-attracting, will promote E_{CO} elimination of the remaining nitrate group, and this effect may therefore occur with the compounds in Tables 2 and 4.

Methyl 2 : 3-di-*O*-acetyl-β-D-glucoside 4 : 6-dinitrate (Table 3) and methyl 2-*O*-acetyl-β-D-glucoside 3 : 4 : 6-trinitrate (Table 5) released less inorganic nitrite than did the corresponding di- and tri-nitrates (Tables 2 and 4 respectively). This is presumably due to the

[7] Bell and Synge, *J.*, 1937, 1711.
[8] O'Meara and Shepherd, *J.*, 1955, 4232.
[9] Baker and Easty, *J.*, 1952, 1208.

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unique position of the 6-nitrate group which, in glucopyranosides, is largely protected from the influence of electrophilic substituents in other parts of the molecule.

Experimental

The nitrates were prepared by previous methods.[7,8] The hydrolyses were carried out in 0·1N-aqueous-methanolic sodium hydroxide as described by Shepherd.[6] In certain experiments (Tables 4 and 5), exactly 1, 2, or 3 mols. of alkali were added.

Isolation of Organic Products.—Hydrolysis of methyl 4 : 6-O-*ethylidene*-β-D-*glucoside* 2 : 3-*dinitrate.* The dinitrate (1·0 g.) was dissolved in methanol (100·0 ml.) and 0·5N-sodium hydroxide (25·0 ml.) was added. After 1 hr. at 22° an aliquot part (1 ml.) was removed for nitrite determination. The excess of alkali was then neutralised with 0·1N-hydrochloric acid, and the mixture concentrated *in vacuo* until crystallisation occurred. The product (0·40 g.) had m. p. 86—87° alone or mixed with the starting material. No other crystalline product could be isolated.

One of us (D. O'M.) is indebted to the Wellcome Research Foundation for a grant.

Department of Pharmacology and Therapeutics,
Queen's College, Dundee. [*Received, March 25th,* 1957.]

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672. *The Thermal Decomposition of α-Lead Azide.*

By P. J. F. Griffiths and J. M. Groocock.

The kinetics of the thermal decomposition *in vacuo* of α-lead azide have been studied by a new technique. With small single crystals of very uniform particle size, initial rapid evolution of gas with an activation energy of 15 kcal. mole^{-1}, due to the decomposition of a surface layer of basic lead carbonate, is followed by the main acceleratory stage of the decomposition characterised by the expression $dV/dt = 10^{8\cdot6}t^4 \exp(-261{,}000/RT)$ (cm.^{3} sec.$^{-1}$ per unit area of crystal surface). Nuclei are produced on the crystal surface according to the expression $dn/dt = 10^{43\cdot5}t \exp(-110{,}000/RT)$ (cm.$^{-2}$ sec.$^{-1}$), and grow three-dimensionally with an interface velocity of $10^{14\cdot3} \exp(-50{,}000/RT)$ (cm. sec.$^{-1}$). Nuclei are thought to be positions where double pairs of positive holes have decomposed to give nitrogen, and nucleus growth occurs by reaction of pairs of positive holes at the nucleus–crystal interface. The decay stage follows a contracting-sphere mechanism.

In thermal decomposition *in vacuo* of single crystals of lead azide weighing 2—4 mg., Garner and Gomm [1] found that the surface of the crystals rapidly became coated with lead and that the subsequent decomposition corresponded to an interface-penetration mechanism. Cleavage of partially decomposed crystals of the α-form showed a well-defined interface. Values between about 30 and 60 kcal. mole^{-1}, with a mean of 47·6, were found for the activation energy of the interface-penetration velocity of the α-form, and between 30 and 50 kcal. mole^{-1}, with a mean of 38·8, for the β-form.

Garner, Gomm, and Hailes [2] analysed pressure–time curves obtained in the decomposition of smaller crystals of lead azide and deduced that the rate in the accelerating stage of the decomposition was proportional to t^m, where m lies between 1 and 3. Hawkes and Winkler [3] in an investigation of the thermal detonation of α-lead azide determined the variation, with temperature, of the time t to reach a fixed degree of decomposition and obtained an activation energy of 37 kcal. mole^{-1} from a plot of log t against $1/T$ (°K). Duke [4] showed by *X*-ray-diffraction experiments that *in vacuo* at 160° C the

[1] Garner and Gomm, *J.*, 1931, 2123.
[2] Garner, Gomm, and Hailes, *J.*, 1933, 1393.
[3] Hawkes and Winkler, *Canad. J. Res.*, 1947, **25**, *B*, 548.
[4] Duke, Ministry of Supply, unpublished results.

β-form slowly changes into the α-form and that the α-form does not undergo a phase change at temperatures below those at which decomposition occurs. Todd [5] by other *X*-ray-diffraction experiments showed that irradiation in air with visible light or *X*-rays changes lead azide to basic lead carbonate and, in the absence of carbon dioxide, to basic lead azide. Well-aged crystals of lead azide always have a surface film of basic lead carbonate. Moore [6] showed that the electrical conductivity of pure α-lead azide in the range 100—140° C is given by the equation $\log \sigma = 0 - 18{,}500/(4{\cdot}576T)$ and that the ultraviolet absorption edge occurs at 3980 Å.

The present investigation has been made with an improved technique and a particularly suitable sample of α-lead azide. The kinetics of the acceleratory and decay stages of the decomposition have been determined and reaction mechanisms are suggested.

Experimental

Materials.—Except where stated otherwise, specimens of the same well-aged sample of α-lead azide were used in all the experiments. The azide was made by a special method by Messrs. A. T. Thomas and G. W. C. Taylor of the Explosives Research and Development Establishment, to whom we are indebted. They have measured the density and specific surface of the material, obtaining values of 4·75 g. cm.$^{-3}$ and 600 cm.^{2} g.$^{-1}$, respectively, and shown that, except for the surface which is chemically changed by ageing processes, the material is of high purity. The sample consisted of single crystals of remarkably uniform particle size and shape. The crystals had a longest dimension of about 45 μ and a section of side 35 μ. By direct count of several 0·1 mg. portions, the sample was found to contain 13,400 crystals per mg.

Apparatus.—The Pyrex-glass apparatus used is illustrated in Fig. 1. It can be evacuated to a pressure of 10^{-6} mm. by a pumping system consisting of a solid carbon dioxide–alcohol trap, an oil diffusion pump, and a rotary oil pump. The reaction chamber *A* is surrounded by a movable furnace *B*. The furnace temperature, controlled by a proportional temperature-controller, is maintained constant to better than ±0·05° C during a run. The pressure in the reaction chamber is measured by a sensitive Pirani gauge *P*, maintained at constant temperature by immersion in solid carbon–dioxide alcohol.

The azide is decomposed on the surface of the copper block *C* in the reaction chamber, and the design is such that the azide is contained in a radiation enclosure at the same temperature as that of the block. That the latter is necessary is shown by experiments in which lead azide crystals were placed on a heated block *in vacuo* but were free to radiate to a surface above them at room temperature. The reaction rate then corresponded to a temperature more than 10° below that of the block. The edges of the block are raised to prevent azide from spilling. The temperature is measured by means of a copper–constantan thermocouple, the hot junction of which is just beneath the centre of the upper surface of the block. The thermocouple was calibrated against a standard mercury thermometer accurate to 0·1°.

The azide samples are contained initially in four small glass buckets mounted on a glass sledge which is free to move along a ground-glass slide *E* fitted to a B45 cone. The buckets are "top-heavy" and kept upright by fins which are in contact with the slide. The cone fits into the socket *F*. The glass-sheathed iron slug *G*, incorporated in the sledge frame, enables the sledge to be pulled along by a permanent magnet. There is a hole in the slide immediately above the reaction chamber, so that when the sledge is pulled over it, consecutive buckets tip, emptying their contents down the guide tube *H* to spread evenly over the surface of the copper block. The buckets strike the slide on tipping, ensuring that no azide is retained.

Procedure.—Each set of four runs was subjected to the following routine. Samples (±0·005 mg.) were loaded into the buckets and the bucket holder was sealed into the apparatus, which was then evacuated to 5×10^{-6} mm. overnight, with the furnace in position and at the desired temperature. Next day, as soon as the reading of the Pirani gauge was steady, the first bucket was tipped and the azide began to decompose with evolution of nitrogen. After the reaction was complete and the apparatus was again in equilibrium, a further run was done. Any samples not used at the end of the day were destroyed, so that all runs were done on samples that had been held in a vacuum of 5×10^{-6} mm. for 19—24 hr.

[5] Todd, Ministry of Supply, unpublished results.
[6] Moore, Ministry of Supply, unpublished results.

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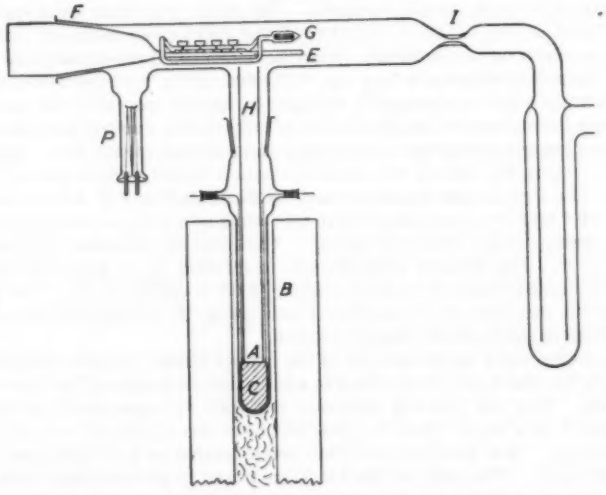
Measurement of Rates.—During a run the rate of decomposition of lead azide is given directly by the rate at which nitrogen is evolved. Because of the constriction *I* in the vacuum line pressure increases in the reaction chamber, being measured by the Pirani gauge and continuously recorded on a photographic trace. For gas pressures at which the mean free path of the molecules is appreciably greater than the minimum diameter of the constriction, the mass flow of gas through the constriction is directly proportional to the pressure difference across it.[7] If, in addition, the pumping rate is such that the pressure on the pump side of the constriction is negligible compared with that on the reaction chamber side, the pressure in the reaction chamber will be directly proportional to the rate of decomposition of the azide for constant rates. Changes in rate cannot be recorded instantaneously because of lags in the pressure gauge and recording equipment and also because of the finite capacity of the reaction chamber. A linear change of rate with time is recorded with a delay equal to the product of the resistance of the orifice (sec. cm.$^{-3}$) multiplied by the volume of the reaction chamber. These lags were not significant for the relatively slow changes of rate of these experiments.

FIG. 1.



The apparatus was calibrated by admitting air into the apparatus at a constant rate and measuring the resulting deflection of the Pirani gauge. If the air is drawn from a small reservoir initially containing a volume V_1 (ml.) at pressure P_1 (atm.), and t seconds later the volume has been reduced to V_2 and the pressure to P_2 (as indicated by an oil manometer), the rate of admission of air is $(P_1V_1 - P_2V_2)/t$ ml. atm. sec.$^{-1}$. If the temperature of the reservoir is known, $(P_1V_1 - P_2V_2)$ can readily be converted into the equivalent weight of lead azide. The gas flow into the apparatus was controlled by a precision needle-valve and for a particular setting the rate of admission remained constant. By varying the needle-valve setting, Pirani gauge deflections corresponding to several different azide decomposition rates were obtained. From these the rate was found to be directly proportional to the deflection, 1 cm. on the Pirani gauge being equivalent to a rate of decomposition of lead azide of $(4{\cdot}1 \pm 0{\cdot}08) \times 10^{-4}$ mg. sec.$^{-1}$. This value includes the small correction required because air rather than nitrogen was used for the calibration.

RESULTS

The thermal decomposition at constant temperature (Fig. 2) commences with an initial rapid evolution of gas, after which the rate falls swiftly. It then increases to a maximum and finally falls off to zero. Measurements of the area beneath the rate–time curve show that complete decomposition has then occurred. Values of log rate were plotted against log time

[7] See, e.g., Dushman, "Scientific Foundations of Vacuum Technique," John Wiley and Sons, New York, 1949, p. 90.

for the early parts of the decomposition and gave a linear relation for the second acceleratory stage. Typical plots are shown in Fig. 3. At *A* (Fig. 3) the effect of the first acceleratory stage is present, *B* is the linear region, and at *C* the final maximum is being approached. For 23 decompositions in the range 285—294° c the slope of the linear regions of these plots showed no systematic variation with temperature. A mean value of 3·94 ± 11% was found.

Values of log $(d\alpha/dt)_\tau$ (taken from the log rate–log time graphs), log *A*, log t_m, and log $(d\alpha/dt)_m$ (taken from the rate–time traces), and log α_m (obtained by measurement of the area under the rate–time traces) gave straight-line plots against $1/T$ (°K). Here $(d\alpha/dt)_\tau$ = rate of decomposition at constant time τ, *A* = the maximum value of the rate of the initial evolution of gas, t_m = time to reach the final maximum rate, $(d\alpha/dt)_m$ = final maximum rate, and α_m = fractional decomposition at maximum rate.

For the decay period of the decomposition, values of both log $(d\alpha/dt)$ and $(d\alpha/dt)^{\frac{1}{2}}$ were plotted against *t*. The curvature of the rate–time traces for this region is not great and at low rates errors produced by drift of the Pirani gauge become significant. It is not unexpected

FIG. 2. *Variation of rate of decomposition (cm. deflection) with time.* *A* = 567·1° K; *B* = 564·4° K; *C* = 559·3° K.

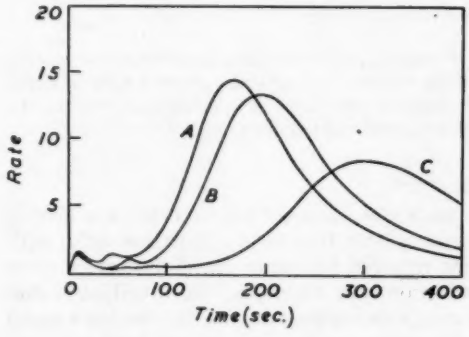
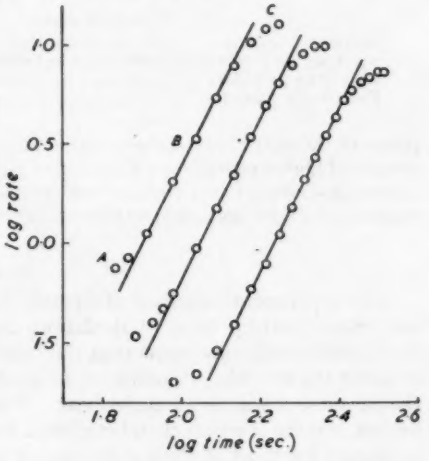


FIG. 3. *Plot of log rate (cm. deflection) against log time at (from left to right)* 566·2° K, 562·4° K, and 558·7° K.



therefore that within the experimental error both plots gave fair straight lines. For different runs log *P* and log *Q*, where *P* is the slope of the $(d\alpha/dt)^{\frac{1}{2}}$–*t* plot and *Q* is the slope of the log $(d\alpha/dt)$–*t* plot, were plotted against $1/T$ (°K). In all cases values of slopes and intercepts, together with their standard deviations, were calculated by the method of least squares on the A.R.D.E. AMOS digital computer. These values, adjusted so that slopes are in the units of activation energy (kcal. mole^{-1}), and intercepts are calculated from rate values in units of sec.$^{-1}$, are given in Table 1. For temperatures below 280° c it was only possible to obtain values of t_m, these being independent of weighing errors and errors due to drift of the Pirani gauge. For t_m the values of the constants obtained from results in the range 262—295° c are little different from those in the range 280—295°, suggesting that the reaction mechanism is essentially the same throughout the wider range. In subsequent calculations the constants from the 280—295° range are used to correspond with the other experimental results.

Other α-Lead Azide Types.—Several other types of α-lead azide were investigated in a more conventional apparatus, in which the azide, contained in a platinum bucket, was lowered into the heated reaction chamber. Activation energies were obtained from values of the maximum rate and these are given in Table 2.

The shape of the decomposition curve in all cases was roughly as described above. For the pure α-lead azide, which had been recrystallised from ammonium acetate, samples of different crystal size were investigated. The maximum rate, for the same temperature and the same

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sample weight, was found to be directly proportional to the surface area of the crystals. For crystals of 240—300 B.S.S. mesh, $(d\alpha/dt)_m$ was 2·5 times that of 60—100 mesh crystals. With this apparatus and with these azide types the experimental reproducibility was not good, and no further quantitative analysis of the decomposition curves was possible.

In other experiments, the surfaces of single crystals of lead azide, thermally decomposing *in vacuo*, were watched through a microscope. The surface darkened and rapidly became black as the decomposition proceeded, but discrete nuclei could not be resolved. The resolving

TABLE 1.

Plot (T in °K)	Slope (kcal. mole^{-1})	Intercept	No. of decompns.	Temp. range (° c)
(*a*) Log t_m against $1/T$	50·4 ± 0·9	−17·1 ± 0·3	41	262—295
(*b*) Log t_m against $1/T$	52·6 ± 1·0	−18·0 ± 0·4	30	280—295
(*c*) Log $(d\alpha/dt)_r$ against $1/T$	−262 ± 11	89·7 ± 4·4	26	280—295
(*d*) Log $(d\alpha/dt)_m$ against $1/T$	−46·6 ± 1·1	15·5 ± 0·4	30	280—295
(*e*) Log α_m against $1/T$	3·3 ± 0·3	−0·89 ± 0·13	16	280—295
(*f*) Log Q against $1/T$	−33·0 ± 4·4	10·4 ± 1·7	16	286—297
(*g*) Log P against $1/T$	−55·3 ± 3·4	19·4 ± 1·3	16	286—297

TABLE 2.

Type of α-lead azide	Activation energy (kcal. mole^{-1})
Service	36
Pptd. in the presence of carboxymethylcellulose	38
Pure (fine particles)	40
Pure (large particles)	52

power of the optical system was better than 10 microns, surface diffraction effects preventing the use of higher resolution. Cleavage of partially decomposed crystals, about 1 mm. in linear dimensions, showed that parts of the crystal remained white and gave some indication of the presence of a lead–lead azide interface, confirming Garner and Gomm's result.[1]

DISCUSSION

The experimental method of tipping the azide alone into the reaction chamber gives a very rapid heat-up time. Calculations assuming heat transfer by radiation only, with black-body conditions, show that the reaction rate will be within 1% of its correct value in about 0·5 second. In addition, heat conduction from the copper block will occur and the gas present will also transfer heat. The more conventional method of lowering a metal bucket into the reaction chamber gives a heat-up time of a few minutes and could not have been used for most of these experiments in which the maximum rate was reached in less than 10 min. During decomposition, heat is produced in the azide by the strongly exothermal reaction and the escape of this heat requires that the temperature of the azide must always be higher by ΔT than that of the reaction vessel. However, if the heat-transfer conditions are good and the reaction rate is not too high, ΔT will be small and the reaction rate will be negligibly different from that corresponding to the measured temperature. In these experiments only about 1 part in 50 of the surface of the copper block was covered with the small crystals and no acceleration of reaction rate attributable to self-heating was observed. In other experiments, at higher temperatures, which will be reported later, self-heating had a significant effect and high reaction rates and detonations were observed. The method of measuring the rate of reaction, apart from its convenience, had the further advantage that the entire decomposition could be followed with the gas pressure always less than 5×10^{-3} mm.

The First Acceleratory Stage.—The azide samples used were " well-aged " and the initial sharp evolution of gas is considered to be due to the decomposition of the surface layer of basic lead carbonate. The slope of the log A againt $1/T$ plot gave an activation energy of 15 kcal. mole^{-1} and this value is probably approximately correct, even though the apparatus was not designed for use with carbon dioxide, because the slope of the plot is independent of the absolute values of A.

The Main Acceleratory Stage.—For the main acceleratory stage of the decomposition the log rate–log time plots had a slope of 4. Combining this with the results of the plot of log $(d\alpha/dt)_\tau$ against $1/T$ gives the variation of the rate of decomposition with time and temperature for this stage by :

$$d\alpha/dt = kt^4 \exp(-E/\boldsymbol{RT}) \text{ (sec.}^{-1}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(i)}$$

where $\log k = 89{\cdot}7 \pm 4{\cdot}4$, $E = 262 \pm 11$ kcal. mole^{-1}, and t (the time of heating) is in seconds. This equation is consistent with a mechanism in which it is supposed (*a*) that reaction nuclei are produced per unit area of crystal surface at a rate proportional to t, *i.e.* :

$$dn/dt = (k_t/t) \exp(-E_t/\boldsymbol{RT}) \text{ (sec.}^{-1}) \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(ii)}$$

where E_t is the activation energy for nucleus formation, and (*b*) that these nuclei grow three-dimensionally into the crystal, the velocity of penetration of the interface being constant at constant temperature, *i.e.* :

$$v = k_g \exp(-E_g/\boldsymbol{RT}) \text{ (cm. sec.}^{-1}) \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(iii)}$$

where E_g is the activation energy for nucleus growth, decomposition occurring at the nucleus–crystal interface. From equations (ii) and (iii) it can readily be shown that the volume of material decomposed at time t per unit area of crystal surface is given by :

$$V = (\pi k_t k_g^3/30t^5) \exp[(-E_t - 3E_g)/\boldsymbol{RT}] \text{ (cm.}^3) \quad . \quad . \quad . \quad . \quad \text{(iv)}$$

and that the rate of decomposition is :

$$dV/dt = (\pi k_t k_g \exp[(-E_t - 3E_g)/\boldsymbol{RT}]/6t^4 \text{ (cm.}^3 \text{ sec.}^{-1}) \quad . \quad . \quad . \quad \text{(v)}$$

dV/dt will be a maximum when the total area of the interfaces between the nuclei and the crystal is a maximum, which will occur at the time of nucleus coalescence. If all the nuclei were the same size and were regularly arranged the number of nuclei per unit area of crystal surface would be :

$$n_c = \tfrac{1}{4} r_c^{-2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(vi)}$$

where r_c is the radius of each nucleus at coalescence, and the total volume of decomposition per unit area would be :

$$V_c = n_c \times \tfrac{2}{3} \pi r_c^3 = \tfrac{1}{12} \pi n_c^{-0{\cdot}5} = \tfrac{1}{6} \pi r_c \text{ (cm.}^3) \quad . \quad . \quad . \quad . \quad \text{(vii)}$$

For the model derived from equations (ii) and (iii) the nuclei will be of different sizes and randomly arranged, but V_c will still be proportional to r_c, where r_c is now the average distance the nucleus interfaces have penetrated into the crystal at coalescence. If a constant h having a value near to unity is added, equation (vii) may be used without introducing any serious error. Integrating equation (ii), assuming that $n = 0$ when $t = 0$, and using equations (iv) and (vii) shows that the time of heating to give nucleus coalescence is :

$$t_c = 0{\cdot}9h^{\frac{1}{4}} k_t^{-\frac{1}{4}} k_g^{-\frac{1}{2}} \exp(\tfrac{1}{4}E_t + \tfrac{1}{2}E_g)/\boldsymbol{RT} \text{ (sec.)} \quad . \quad . \quad . \quad . \quad \text{(viii)}$$

Equations (iv), (v), and (viii) can be used to obtain the following expressions for V_c and the rate of decomposition at coalescence, $(dV/dt)_c$:

$$V_c = 0{\cdot}4h^{\frac{1}{2}} k_t^{-\frac{1}{4}} k_g^{\frac{1}{2}} \exp(\tfrac{1}{4}E_t - \tfrac{1}{2}E_t)/\boldsymbol{RT} \text{ (cm.}^3) \quad . \quad . \quad . \quad . \quad . \quad \text{(ix)}$$

$$(dV/dt)_c = 1{\cdot}2h^{\frac{1}{2}} k_g \exp(-E_g/\boldsymbol{RT}) \text{ (cm.}^3 \text{ sec.}^{-1}) \quad . \quad . \quad . \quad . \quad \text{(x)}$$

V_c being known, equation (vii) enables values of n_c and r_c to be obtained.

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Equations (v), (viii), and (ix) can be used with the results of plots (*c*), (*b*), and (*e*) (Table 1), to give the following relations between k_1, E_1, k_2, and E_2.

$$\log (\tfrac{1}{6}\pi k_t k_g^3) = 89{\cdot}7 - 3{\cdot}5 \pm 4{\cdot}4$$

$$-E_t - 3E_g = -262 \pm 11 \text{ (kcal. mole}^{-1}\text{)} \quad \text{(xi)}$$

$$\log (0{\cdot}9h^{\frac{1}{2}}k_t^{-\frac{1}{2}}k_g^{-\frac{1}{2}}) = -18{\cdot}0 \pm 0{\cdot}4$$

$$\tfrac{1}{4}E_t + \tfrac{1}{2}E_g = 52{\cdot}6 \pm 1{\cdot}0 \text{ (kcal. mole}^{-1}\text{)} \quad \text{(xii)}$$

$$\log (0{\cdot}4h^{\frac{1}{2}}k_t^{-\frac{1}{2}}k_g^{\frac{1}{2}}) = -0{\cdot}89 - 3{\cdot}5 \pm 0{\cdot}13$$

$$\tfrac{1}{4}E_t - \tfrac{1}{2}E_g = 3{\cdot}3 \pm 0{\cdot}3 \text{ (kcal. mole}^{-1}\text{)} \quad \text{(xiii)}$$

The solutions of these equations together with mean values are given in Table 3, showing very good agreement. In addition equation (x) and plot (*d*) give values of log k_g and E_g

TABLE 3.

Equations	log k_t	E_t (kcal. mole^{-1})	log k_g	E_g (kcal. mole^{-1})
(xi) and (xii)	42·4	107·2	14·7	51·6
(xi) and (xiii)	44·2	112·7	14·1	49·8
(xii) and (xiii)	44·0	111·8	14·0	49·3
Mean	43·5	110·0	14·3	50·2

of 46·6 and 12·0 respectively. These values are slightly different from those of Table 3 because $(dV/dt)_c$ will be much more sensitive to the approximations of equation (vii) than either t_c or V_c. The values given in Table 2 indicate that E_g varies appreciably for different lead azide types, but this conclusion is open to doubt in view of the experimental difficulties found with these materials. The rate equation (v) can now be given as $dV/dt = (10^{86}/t^4) \exp(-261{,}000/RT)$ (cm.^{3} sec.$^{-1}$ per unit area of crystal surface). Experimentally, α_c has a mean value of about 0·4 over the temperature range investigated. For this value log $V_c = -3{\cdot}9$, $n_c = 10^{8{\cdot}6}$ nuclei per unit area of crystal surface, and $r_c = 2{\cdot}4$ μ, so that discrete nuclei could not have been resolved in the microscopic investigation. The activation energy of 3·3 kcal. mole^{-1} corresponds to a change of V_c of about 5% in the temperature range 262—295° C, and r_c would be doubled by a reduction of the decomposition temperature by about 135°.

If V_c is the same for the crystals investigated by Garner and Gomm and for the sample investigated in this work, the values of α_c for the two samples will be in the ratio of their specific surface. From the crystal size used by Garner and Gomm, α_c may be calculated to be about 0·007, the acceleratory stage being negligible, as found.

Mechanism of Nucleus Formation.—The rate of nucleus formation per unit area of crystal surface has been shown to be given by the equation $dn/dt = (k_t/t) \exp(-E_t/RT)$ (sec.$^{-1}$), where log $k_t = 43{\cdot}5$ and $E_t = 110$ kcal. mole^{-1}. The mechanism of nucleus formation will almost certainly involve electronic transitions from the full band of the azide ion either to the conduction band or to an exciton level. Seitz [9] has suggested that, unlike the alkali bromides, silver bromide has its lowest conduction band level below its exciton level. The same may be true for the heavy-metal azides, and the very great differences between the ultraviolet absorption spectra of silver and lead azides, and the alkaline-earth azides, together with the much higher photoconductivity of the heavy-metal salts supports this. Further, Groocock [10] has found that in the ultraviolet photolysis of α-lead azide the rate of decomposition is proportional to the intensity of irradiation and has explained his results

[9] Seitz, *Rev. Mod. Phys.*, 1951, **23**, 328.
[10] Groocock, Ministry of Supply, unpublished report, 1954.

in terms of a positive-hole mechanism, whereas Thomas and Tompkins [11] found that the photolysis rate of barium azide was proportional to the square of the intensity of irradiation and used an exciton mechanism to explain this. It is therefore probable that the mechanism of the thermal decomposition of lead azide depends upon the production of positive holes rather than excitons. Lead azide has a very much higher enthalpy of formation than the alkaline-earth azides,[12] and it absorbs light at much longer wavelength, implying that the necessary energy for electronic transitions is lower. These factors should make lead azide less stable than the alkaline-earth azides, but in fact lead azide does not decompose appreciably at temperatures below 250° whereas the alkaline-earth azides decompose in the range 100—120°. The stability of lead azide may arise from dependence of its decomposition on reaction between positive holes, this requiring a high activation energy because of the electrostatic repulsion forces to be overcome. A mechanism of nucleus formation which depends upon reaction of positive holes and gives good agreement with the experimental results will therefore be described.

On the surface an equilibrium between positive holes and azide ions will rapidly be attained, *i.e.*, in the reaction $N_3^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} N_3 + e$, when $k_1(N_3^-) = k_2(N_3)(e)$. If $(N_3) \ll (N_3^-)$, $(N_3) = (k_1N/k_2)^{\frac{1}{2}}$, and this condition will be satisfied if $(k_1/k_2N)^{\frac{1}{2}} \ll 1$. Here N is the total number of azide ions per unit area of crystal surface ($\sim 10^{15}$). The positive holes will be mobile and it is suggested that reaction to give three molecules of nitrogen will occur whenever collision takes place between two positive holes with the necessary activation energy, *i.e.*, $dp/dt = k_3(N_3)^2$, where p is the concentration per unit area of positions where this decomposition has taken place. If this concentration is zero at the time heating commences, $p = k_3(N_3)^2t$. The rate of production of nuclei, *i.e.*, places where this decomposition has occurred in neighbouring positions, will be given by $dn/dt = (2bp/N)\,dp/dt$, where b is the number of positions adjacent to a decomposition position, in which decomposition will result in nucleus formation. The rate of nucleus formation is now given by $dn/dt = 2b(k_1k_3/k_2)^2Nt$ (cm.$^{-2}$ sec.$^{-1}$), which is of the form of the experimental equation (ii).

In this equation, k_1 may reasonably be given by $k_1 = \gamma \exp(-E_1/RT)$, where γ is the lattice vibration frequency ($\sim 10^{13}$ sec.$^{-1}$) and E_1 is the activation energy for positive-hole formation. k_2 is likely to have a very low activation energy and it may be assumed that a conduction-band electron will be trapped if it passes within one or two ionic radii of a hole, say, within 10^{-7} cm. If the electrons have thermal energy their velocity will be about 10^7 cm. sec.$^{-1}$ at 550° K, so that $k_2 \sim 1$. k_3 will depend upon a similar interaction between two positive holes, and because of the lower mobility of these compared with conduction-band electrons will probably have a velocity about an order less. In this case an activation energy E_3 will be required for reaction, so that $k_3 \simeq 0{\cdot}1 \exp(-E_3/RT)$. The rate of production of nuclei is now given by: $dn/dt \simeq (10^{40}/t) \exp[-2(E_1 + E_3)/RT]$ (cm.$^{-2}$ sec.$^{-1}$). In view of the approximations made, the pre-exponential term is in reasonable agreement with the experimental value for k_t of $10^{43{\cdot}5}$. From the exponential term $E_1 + E_3 =$ 55 kcal. mole^{-1}. For barium azide Thomas and Tompkins [13] assume that absorption of light at 2600 Å gives rise to the electron transition from the full to the conduction band and calculate that the corresponding thermal activation energy should be 35—48 kcal. mole^{-1}. The same calculation applied to α-lead azide gives the value $E_1 = 22$—30, and from this $E_3 = 25$—33 kcal. mole^{-1}.

The validity of some of the assumptions made in this derivation can now be considered. The expression $(N_3) = (k_1/N/k_2)^{\frac{1}{2}}$ is true if $(k_1/k_2N)^{\frac{1}{2}} \ll 1$, and from the calculated values it can be shown that $(k_1/k_2N)^{\frac{1}{2}} < 10^{-6}$. The concentration of positive holes will be lower than is given by the equilibrium reaction because positive holes are being destroyed continually

[11] Thomas and Tompkins, *Proc. Roy. Soc.*, 1951, *A*, **209**, 550.
[12] Gray and Waddington, *ibid.*, 1956, *A*, **235**, 106.
[13] Thomas and Tompkins, *J. Chem. Phys.*, 1952, **20**, 662.

by decomposition. However, from the values calculated above, it can be shown that for the reaction $N_3^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} N_3 + e$ starting with $(N_3) = 0$, (N_3) is within 99% of its equilibrium value of 10^9 cm.$^{-2}$ in 3×10^{-9} sec., whereas the overall process is slow, the whole acceleratory stage of the decomposition taking many seconds. Therefore, in any region in which a decomposition centre is formed the equilibrium concentration of positive holes will be restored extremely rapidly.

Mechanism of Nucleus Growth.—In the preceding sub-section the nuclei for decomposition were characterised as positions where decomposition of four azide ions had occurred. The residue of two lead atoms or lead ions and associated *F*-centres is thought to function as a decomposition nucleus because the activation energy for positive-hole formation will be reduced in its vicinity, electrons being excited from the full band of the azide lattice to the metal nucleus rather than to the conduction band, and the reverse reaction will be inhibited. In the interface decomposition is thought to proceed, as in nucleus formation, by the bimolecular reaction of positive holes, the reaction mechanism being $N_3^- \underset{k_2^1}{\overset{k_1^1}{\rightleftharpoons}} N_3 + e$ and $2N_3 \xrightarrow{k_3^1} 3N_2$. The decomposition exposes another layer of azide ions to the interface and therefore for unit area of interface $(N_3^-) + (N_3) = N$ (a constant). The velocity of progression of the interface is constant, so that the attainment of equilibrium can be assumed, *i.e.*, $d(N_3)/dt = k_1^1(N_3^-) - k_2^1(N_3)(e) - k_3^1(N_3)^2 = 0$, $(N_3) = (e)$, and $(N_3) \ll (N_3^-)$, so that $(N_3)^2 = k_1^1 N/(k_2^1 + k_3^1)$ and the reaction rate $= k_3^1(N_3)^2 = k_1^1 k_3^1 N/(k_2^1 + k_3^1)$. The velocity of penetration of the interface is then $v = \sigma k_1^1 k_3^1/(k_2^1 + k_3^1)$, where σ is the thickness of an ionic layer (4×10^{-8} cm.). Now $k_1^1 = \gamma \exp(-E_1^1/\boldsymbol{RT})$, where E_1^1 is the activation energy for excitation of an electron from an azide ion to the metal nucleus, and $k_3^1 \simeq k_3 = 0{\cdot}1 \exp(-E_3/\boldsymbol{RT})$. It is to be expected that $k_2^1 < k_2$, say $k_2 = xk_2^1$, and it is likely that $k_2^1 \gg k_3$, so that

$$v \sim 4 \times 10^4 x \exp[-(E_1^1 + E_3)/\boldsymbol{RT}] \text{ (cm. sec.}^{-1}\text{)}.$$

Experimentally $E_1^1 + E_3 = 50{\cdot}2$ kcal. mole^{-1}, whereas $E_1 + E_3 = 55$ kcal. mole^{-1}, and $E_1^1 < E_1$, as is expected. The value of x may be sufficiently high for the pre-exponential term to approach the value of 4×10^5 cm. sec.$^{-1}$ given by simple application of the Polanyi–Wigner equation. It is, however, very much below the experimental value and this suggests that in the reaction $2N_3 \xrightarrow{k_3^1} 3N_2$ the activated complex has a very disordered structure so that a big increase in entropy results.

The Decay Stage.—As the early stages of the decomposition proceed by a mechanism of nucleus formation and growth on the crystal surface it is to be expected that after coalescence of the nuclei the decomposition will be controlled by the rate of penetration of the lead–lead azide interface into the crystal. At nucleus coalescence the particles used in this work can be considered to be identical spheres of undecomposed azide surrounded by a metallic layer. If the interface moves at a constant velocity, *i.e.*, $dr/dt = -k$, where r is the radius of each sphere at time t, the rate of decomposition is $d\alpha/dt = 4\pi r^2(dr/dt)c\rho$, where c is the number of particles in unit weight of the sample and ρ is the density of lead azide. If the radius of the particles is a at time τ it can readily be shown that $(d\alpha/dt)^{\frac{1}{3}} = (4\pi c\rho k)^{\frac{1}{3}}(a + k\tau) - (4\pi c\rho)^{\frac{1}{3}}k^{\frac{4}{3}}t$, and a plot of $(d\alpha/dt)^{\frac{1}{3}}$ against t should give a straight line, as found experimentally. The slope of this line, $P = -(4\pi c\rho)^{\frac{1}{3}}k^{\frac{4}{3}}$, is independent of a and τ and is therefore unaffected by the acceleratory stage variation of V_0 with temperature. k is given by $k = k_1 \exp(-E_1/\boldsymbol{RT})$, so that a plot of log P against $1/T$ will give an activation energy of $\frac{4}{3}E_1$ and a pre-exponential term of $(4\pi c\rho)^{\frac{1}{3}}k_1^{\frac{4}{3}}$. From the experimental values given in plot (*g*) (Table 1), $k_1 = 10^{10}$ cm. sec.$^{-1}$ and $E_1 = 37$ kcal. mole^{-1}. These values are not in very good agreement with the corresponding terms k_g and E_g for the nucleus-growth stage, but the values resulting from the assumption of a unimolecular process for the decay stage (plot *f*, Table 1) are slightly worse and the standard deviation

is twice as large. These facts and the supporting evidence, *e.g.*, the microscopic evidence for a lead–lead azide interface, indicate that the contracting-interface mechanism is probably correct, although the simple treatment used here in which the particles are assumed to be spheres of uniform size, may not be strictly applicable.

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MINISTRY OF SUPPLY, ARMAMENT RESEARCH AND DEVELOPMENT ESTABLISHMENT,
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673. *The Separation of Lactones from Reducing Sugars by Anion-exchange Resins.*

By GREVILLE MACHELL.

The carbonate form of the strong-base resins De-Acidite FF micro-bead with 2% of cross linking has been shown to be suitable for the separation of lactones from reducing sugars.

DURING an investigation into the alkaline degradation of carbohydrates, the need arose for a method by which sugar acids could be separated from reducing sugars. An ion-exchange procedure was an obvious choice, but the situation was complicated by a number of factors. The acids in question existed in solution in equilibrium with their lactones, and preliminary experiments showed that, although the free acid was quite readily taken up on a column of an anion-exchange resin in the free-base form, sorption of the lactone was incomplete. This difficulty has already been reported by Berntsson and Samuelson [1] for sorption of gluconic acid on the weak-base resin Dowex-3, the lactone being completely taken up when stirred with an excess (unspecified) of the resin for 24 hours.

The choice of an anion-exchange resin is at once limited by the presence of alkali-labile reducing sugar. Thus, while for efficient sorption of the lactone, a strong-base resin would be preferred, the presence of a reducing sugar rules this out. Phillips and Pollard [2] showed that glucose and other sugars were strongly sorbed and rapidly degraded by the strong-base resin Amberlite IRA-400. However, Bryant and Overell [3] had noted that reducing sugars were not sorbed to an appreciable extent by Amberlite IRA-400 in the carbonate form, and that this could be used in a column for separation of acids such as citric, malic, and succinic from reducing sugars.

A further factor to be considered was the effect of the physical state of the resin on the sorption of a given lactone. Commercial anion-exchange resins are normally supplied in a particle size varying from *ca.* 0·25 to 1·0 mm. and, for these resins which are based on polystyrene, with a *ca.* 10% cross-linking of the polystyrene matrix. The rate and extent of sorption of large organic ions should be increased by reducing the particle size of the resin, and also by reducing the cross-linking to a nominal 2%, which is the lowest practical value.

It has now been found that the carbonate form of the strong-base resin De-Acidite FF micro-beads with 2% of cross linking gives satisfactory sorption of a number of lactones when it is stirred with their aqueous solutions for 24 hours and when the amount of lactone does not exceed *ca.* 10—15% of the theoretical exchange capacity of the resin. Further, recovery of the sorbed material was very high when aqueous ammonium carbonate was used as the eluant (see Table 1). These results contrast sharply with the result obtained on sorption of α-D-gluco*iso*saccharinolactone on the same resin in a *column*, the extent of

[1] Berntsson and Samuelson, *Acta Chem. Scand.*, 1955, **9**, 277.
[2] Phillips and Pollard, *Nature*, 1953, **171**, 41.
[3] Bryant and Overell, *ibid.*, 1951, **167**, 361.

sorption of the lactone being then only 48%, compared with 92% for the batch method with similar quantities.

Experiments with glucose, fructose, and xylose established that this carbonate resin had no measurable affinity for reducing sugars, and was without effect on such sugars in solution.

As a final demonstration of its suitability, a synthetic mixture of α-D-gluco*iso*saccharinolactone with a large excess of glucose was completely separated, and a 91% recovery of lactone achieved.

The two weak-base resins Amberlite IR-4B(OH) and De-Acidite G in the free-base form were also investigated. It is clear from the results in Table 1 that these resins do not take up the lactones satisfactorily, and that the sorbed material is not readily eluted. Further, both resins sorbed glucose from aqueous solution, as recorded by Reynolds [4] for Amberlite IR-4B(OH).

TABLE 1. *Sorption of lactones on anion-exchange resins.*

Resin (5 g.)	Lactone	Acid + lactone (milliequiv.)	Lactone (%)	Sorption of acid + lactone (%)	Elution of sorbed acid (%)
Amberlite IR-4B(OH)	D-Glucono-δ-lactone	5·1	*	98	82
	α-D-Gluco*iso*saccharinolactone	2·65	71	89	54
De-Acidite G, free base (−16 + 50 mesh)	D-Glucono-δ-lactone	5·1	*	84	*
	α-D-Gluco*iso*saccharinolactone	2·35	70	69	*
De-Acidite G, free base (micro-bead, 2% cross-linked)	D-Glucono-δ-lactone	5·1	*	97	35
	α-D-Gluco*iso*saccharinolactone	2·4	68	74	53
De-Acidite FF, carbonate form (−16 + 50 mesh)	D-Glucono-δ-lactone	5·1	*	100	90
	α-D-Gluco*iso*saccharinolactone	2·4	79	76	*
De-Acidite FF, carbonate form (micro-bead, 2% cross-linked)	D-Glucono-δ-lactone	5·1	*	99	97
	α-D-Gluco*iso*saccharinolactone	5·3	71	56	*
	" "	2·65	71	92	95
	" "	1·58	79	100	97
	α-D-Glucosaccharinolactone	2·45	83	95	98
	β-D-Gluco*meta*saccharinolactone	2·5	66	95	99
	D-Saccharolactone	1·9	23	99	95
	Lactobionolactone	2·28	5	97	90

* Not determined.

It is of interest to examine the difference in behaviour of the various lactones investigated, as revealed by the extent of sorption of each lactone on different anion-exchangers. The extent of sorption of D-glucono-δ-lactone was practically independent of the resin employed. This is evidently due to the rapid hydrolysis of this lactone to the free acid in aqueous solution, the hydrolysis being followed by a relatively slow formation of the γ-lactone (see Table 2). These observations agree with earlier measurements [5] of the optical

TABLE 2. *Hydrolysis of* D-*glucono-δ-lactone.*

Time (hr.)	0	0·25	0·5	1·0	2·0	4	7	23·5	48
Lactone (%)	100·0	70·0	56·4	42·8	24·7	12·2	5·4	8·1	15·0

rotation of aqueous solutions of D-glucono-δ-lactone. Thus one is obviously concerned here with direct sorption of the free acid by the resin, hydrolysis of the δ-lactone to the free acid being accelerated by removal of the latter from the system by sorption as soon as it is formed. Lactobionolactone almost certainly behaves in a similar manner.

In contrast, the three D-glucosaccharinolactones were stable in solution. Thus, when

[4] Reynolds, *Nature*, 1955, **175**, 46.
[5] Isbell and Frush, *J. Res. Nat. Bur. Stand.*, 1933, **11**, 649.

the free acid was completely removed from an acid–lactone mixture by passage through a column of De-Acidite FF carbonate, no free acid was detected in the resulting lactone solution, even after 5 days at room temperature. It is clear that for these three lactones sorption by anion-exchange resins should take place less readily, and this conclusion is in accord with the experimental results. Whether the D-glucosaccharinolactones are sorbed directly by the resin, or the resin catalyses a prior hydrolysis to the free acids, remains to be established.

Experimental

The following solvents and sprays were used for chromatography with Whatman No. 1 paper at 25°. Solvents: A, ethyl acetate–acetic acid–water (10 : 1·3 : 1); B, butan-1-ol–pyridine–water (6 : 4 : 3). Sprays: a, silver nitrate–sodium hydroxide;[6] b, B.D.H. 4·5 indicator;[7] c, *p*-anisidine hydrochloride;[8] d, hydroxylamine–ferric chloride.[9]

Preparation of Lactones.—D-Glucono-δ-lactone was a commercial sample whose purity was checked by titration. α-D-Gluco-, α-D-gluco*iso*- and β-D-gluco*meta*-saccharinolactone, and D-saccharolactone were prepared by treating the calcium salt of the appropriate acid with an excess of washed Amberlite IR-120(H) resin to remove calcium, and finally heating the aqueous solution at *ca.* 70° for 1 hr. in the presence of the resin to bring about lactonisation. Lactobionolactone was obtained from the calcium salt as indicated, but the heating was omitted to avoid hydrolysis of the glycosidic link. The amount of acid + lactone present in each solution was determined by the addition of a two-fold excess of standard alkali, storage for 30 min. at 20° to decompose lactones, and back-titration with acid. Where appropriate, the amounts of free acid and lactone in solution were determined by direct titration with alkali to bromothymol-blue.

Preparation of Ion-exchange Resins.—Amberlite IR-4B(OH) was supplied in the free-base form and was freed from small amounts of chloride by washing in a column with a 2% solution of sodium carbonate. De-Acidite G (−16 + 50 mesh) was supplied in the chloride form, and was converted into the free-base form by washing with 3% ammonia solution. After the resin (80 g.) in a column had been treated with ammonia (3 l.) during 48 hr., appreciable amounts of chloride ion were still being removed. De-Acidite G (micro-beads, 2% cross-linked) was freed from fine material and treated as the large beads.

De-Acidite FF (−16 + 50 mesh) was converted into the carbonate form by treatment with a large excess of N-aqueous ammonium carbonate. The prepared resin still contained a small amount of chloride ion.

De-Acidite FF (micro-beads, 2% cross-linked) was freed from fines and converted into the carbonate form as above. The prepared material was free from chloride ion. Amberlite IR-120(H) was washed with distilled water until the effluent was free from chloride ions.

" AnalaR " or " Micro-analytical reagents (M.A.R.) " reagents were used in this and subsequent work.

Sorption of Lactones on Anion-exchange Resins.—An aqueous solution (50 ml.) (100 ml. for D-gluconolactone) of the acid–lactone mixture in amount as indicated in Table 1 was stirred with the air-dried resin (5 g.) for 24 hr. at room temperature. The resin was then transferred to a column, and the lactone remaining in the filtrate determined by titration as indicated previously. Sorbed material was eluted from the resin during 1 hr. with N-ammonium carbonate (100 ml.), except for the experiments in which Amberlite IR-4B(OH) was used, when the eluant was 2% aqueous sodium carbonate (250 ml.). The eluate was run directly on to a stirred suspension of Amberlite IR-120(H) (60 g.) to decompose excess of ammonium carbonate and the ammonium salt of the eluted acid. Removal of traces of ammonium ions was completed by passage of the acid solution through a column of the same resin (5 g.). With all the resins except De-Acidite FF carbonate (micro-beads, 2% cross-linked) the final acid solution was found to contain chloride ions eluted from the resin. These ions were eliminated by neutralisation of the solution with silver carbonate, and removal of the precipitated silver chloride by filtration. The free acid was then recovered by running the solution of the silver salt through a column of Amberlite IR-120(H) (5 g.), and the acid in the effluent determined as described. Results are recorded in Table 1.

[6] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.
[7] Nair and Muthe, *Naturwiss.*, 1956, **43**, 106.
[8] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[9] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

Sorption of α-D-Glucoisosaccharinolactone on De-Acidite FF Carbonate (Micro-beads, 2% Cross-linked) in a Column.—A solution of α-D-glucoisosaccharinolactone (2·4 milliequiv., 78% of lactone) in water (50 ml.) was run through a narrow (0·8 cm.) column of De-Acidite FF carbonate (micro-beads, 2% cross-linked) during 2·5 hr. The time taken for this operation was about five times longer than that usually accepted as adequate.[6] Titration of an aliquot part of the effluent and washings as described showed that only 1·15 milliequiv. (48%) of the original acid + lactone had been sorbed. Direct titration with alkali of a second portion established the absence of free acid, and from the two determinations it follows that the extent of sorption of the *lactone* was only 33%.

Sorption of Reducing Sugars on Anion-exchange Resins.—Amberlite IR-4B(OH). A solution of glucose (5 g.) in water (500 ml.) was run through a column of Amberlite IR-4B(OH) (5 g.). After the column had been washed with distilled water (6 l.) during 18 hr. sorbed glucose was eluted with a 2% sodium carbonate solution (180 ml.), and sodium ions were removed from the eluate with Amberlite IR-120(H) in batch and column as above. After elimination of chloride ions with silver carbonate as described, the solution was concentrated, under reduced pressure at room temperature, for paper chromatography. By using solvent A and sprays a and b, the presence of a considerable amount of glucose, but no acidic or neutral degradation products, was established.

De-Acidite G (*−16 + 50 mesh*). A solution of glucose (1 g.) in water (50 ml.) was stirred with De-Acidite G (5 g.) for 24 hr. After transference of the resin to a column, a portion of the solution was evaporated to small bulk and retained for chromatographic examination. The resin was then eluted with N-ammonium carbonate (100 ml.), and ammonium and chloride ions were removed as before. A portion of the eluate was then concentrated for chromatography.

Paper chromatography of the non-sorbed material and the eluate in solvent B, and application of sprays a and c, resulted in the detection of glucose only in the non-sorbed material, and a significant amount of glucose in the eluate. Further chromatography of the eluate in solvent A, and the use of sprays b and d, failed to detect any acids or lactones.

De-Acidite FF *carbonate* (*micro-beads, 2% cross-linked*). The behaviour of glucose, fructose, and xylose was investigated. The sugar (1 g.) was stirred with De-Acidite FF carbonate (micro-beads, 2% cross-linked) (5 g.) for 24 hr., and the resin separated from the non-sorbed sugar. Sorbed sugar was then recovered by elution as indicated, except for a simplification due to the absence of chloride ion in the eluate. In all three cases, paper chromatography of the non-sorbed material in solvent B, and the use of sprays a and c, detected nothing other than the original sugar. The eluates from the three experiments were chromatographed in solvents A and B, with sprays b and a, respectively. Neither the original sugar nor any degradation product was detected in the eluates. Testing with Tollens's reagent did reveal a trace of original sugar in the eluates from the fructose and xylose experiments, but comparison with standards showed that the amount of sugar present in the total eluate in both cases was certainly <1 mg.

Separation of Glucose and α-D-Glucoisosaccharinolactone using De-Acidite FF *Carbonate (Micro-beads, 2% Cross-linked).*—A mixture of glucose (2 g.) and α-D-glucoisosaccharinolactone (3·15 milliequiv., 79% lactone) in water (100 ml.) was stirred with De-Acidite FF carbonate (micro-beads, 2% cross-linked) (10 g.) for 24 hr. at room temperature. The resin was then transferred to a column and washed with water, and the combined filtrate and washings (1 l.) were concentrated to exactly 250 ml. under reduced pressure at room temperature. Non-sorbed lactone was determined by titration, and a correction applied for the small amount of acid formed from the glucose present. Sorption of the lactone was found to be virtually complete (99%). Chromatography of the non-sorbed material in solvent B, with sprays a and c, revealed the presence only of glucose.

The sorbed material was eluted from the resin during 2 hr. with N-ammonium carbonate (200 ml.), and the excess of eluant removed by evaporation to a thin syrup under reduced pressure. Passage of the diluted syrup (50 ml.) through a column of IR-120(H) (10 g.) resulted in the break-up of the ammonium salt to give a solution of the free acid. This modification in the treatment of the eluate economises in the use of IR-120(H) and thus eliminates a possible source of contamination of the solution with chloride ion. However, it can obviously be applied only when the eluate is known to be free from alkali-labile material. By titration of an aliquot part of the acid solution, the total acid present was found to be 2·84 milliequiv. A second elution of the resin with a similar amount of ammonium carbonate removed only a further 0·02

milliequiv. of acid. From these figures, the efficiency of elution of the sorbed acid was found to be 92%, and the recovery of the original acid 91%.

Paper chromatography of the eluate with solvent B and sprays a and c failed to reveal any glucose. With solvent A and sprays b and d, only α-D-gluco*iso*saccharinic acid and its lactone were detected.

Hydrolysis of Lactones.—D-*Glucono*-δ-*lactone*. This lactone (0·890 g., 5 milliequiv.) was dissolved in water (100 ml.) at 20°. At suitable intervals, aliquot parts of the solution were removed, and the free acid formed by hydrolysis was determined by a rapid direct titration with alkali. Results are given in Table 2.

D-*Glucosaccharinolactones*. Solutions of α-D-gluco-, α-D-gluco*iso*-, and β-D-gluco*meta*-saccharinolactone (*ca.* 2 milliequiv.) were obtained from the calcium salts of the parent acid as described. The solution of each lactone (50 ml.) was then run through a column of De-Acidite FF carbonate (−16 + 50 mesh) (5 g.) during 0·5 hr. This resulted in the sorption of all of the free acid and a small amount of the lactone, leaving a solution of the pure lactone. Titration of aliquot parts of each lactone solution failed to detect any free acid, even after the solution had been kept for 5 days at room temperature.

The author is grateful to the Permutit Co. Ltd., for the gift of the De-Acidite anion-exchange resins used in this work, to Dr. T. V. Arden for helpful discussion, and to Dr. G. N. Richards for his interest and advice. This work forms part of the programme of fundamental research undertaken by the Council of the British Rayon Research Association.

THE BRITISH RAYON RESEARCH ASSOCIATION, HEALD GREEN LABORATORIES, WYTHENSHAWE, MANCHESTER, 22. [*Received, March 30th*, 1957.]

[10] See, *e.g.*, Samuelson, "Ion Exchangers in Analytical Chemistry," Wiley, New York, 1953, p. 95.

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674. *Photodehydrogenation and Photo-oxidation of Some Thermochromic Ethylenes and Related Compounds.*

By ABDEL FATTAH ALY ISMAIL and ZAKI MOHAMMED EL-SHAFEI.

A new type of thermochromic ethylene (I) is photo-oxidised in presence of oxygen, giving anthraquinone and fluorenone; it is not affected by sunlight in a carbon dioxide atmosphere. In the early stages of the reaction a peculiar reversible colour change was achieved. On the other hand, a related compound (V) and a derivative (VI) are photodehydrogenated in presence of oxygen or carbon dioxide with the formation of highly condensed ring-systems.

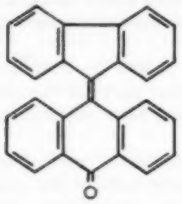
THERMOCHROMISM and piezochromism exhibited by certain polynuclear ethylenes, *e.g.*, dianthraquinone and dixanthylidene, have been attributed to diradical formation [1] or internal betaine structure.[2]

We here report a new thermochromic ethylene, 9-9′-fluorenylideneanthrone (I), a yellowish-brown solid (violet melt) which gives deep violet solutions that exhibit thermochromism. When pressed, the crystals change to deep violet (piezochromism). The fact that it suffers photo-oxidation with cleavage to anthraquinone and fluorenone (the first case of this type in thermochromic ethylenes) seems to favour the existence of a diradical whose formation is enhanced by irradiation. Acceleration of oxygen absorption with time

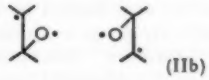
[1] Ingold and Marshall, *J.*, 1926, 3080; Schönberg and Schütz, *Ber.*, 1928, **61**, 478; Bergmann and Engel, *Z. phys. Chem.*, 1930, **8**, *B*, 135; Bergmann and Corte, *Ber.*, 1933, **66**, 39; Schönberg, Kaltschmidt, and Schulten, *ibid.*, 1933, **66**, 247; Bergmann, "Isomerism and Isomerisation of Organic Compounds," John Wiley and Sons, Inc., New York, 1948, p. 47; Grubb and Kistiakowsky, *J. Amer. Chem. Soc.*, 1950, **72**, 419; Theilacker, Kortüm, and Friedheim, *Ber.*, 1950, **83**, 508; Le Fèvre and Youhotsky, *J.*, 1953, 1318.

[2] Schönberg, Ismail, and Asker, *J.*, 1946, 442.

(Table) indicates that the compound is producing a fresh chain-starting catalyst (IIa or b) and forming a peroxide; although it was not isolated, its presence was revealed by the

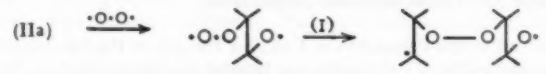


(I)



(IIa) (IIb)

peculiar reversible colour change which was noticed in the early stages of the photo-oxidation. This colour change is more or less similar to that given by hexaphenylethane.[3]



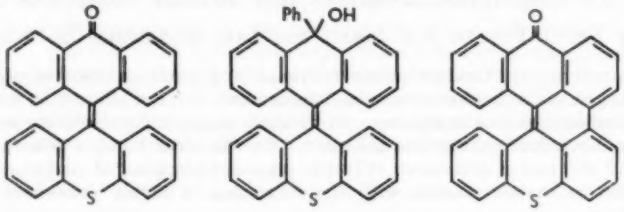
(IIa) (III) (IV)

Of several possible mechanisms for the photochemical cleavage by oxygen, reaction by way of the peroxide (IV) is favoured: the radical (IIb) supposed to be formed then, like (IIa), undergoes a similar chain reaction.

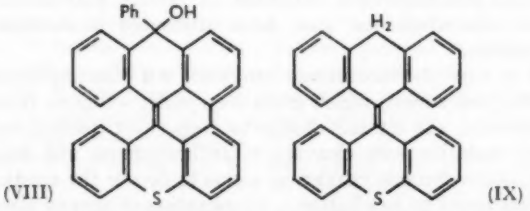
$$\text{(IV)} \longrightarrow \text{Anthraquinone} + \text{Fluorenone} + \text{(IIb)}$$

Photo-oxidation of the compound (I) is somewhat similar to the autoxidation of bis-diphenylene-ethylene [4] and the photo-oxidation of polystyrene peroxide.[5]

The compound (I) was not affected by sunlight in a carbon dioxide atmosphere or in the dark in presence of oxygen; its photo-oxidation was inhibited in presence of *p*-benzoquinone.[4] On the other hand, 10-9′-thiaxanthylideneanthrone (V) and its Grignard



(V) (VI) (VII)



(VIII) (IX)

product, 9 : 10-dihydro-9-phenyl-10-10′-thiaxanthylideneanthran-9-ol (VI), were dehydrogenated on irradiation in either oxygen or carbon dioxide, yielding the benzo[*a*, *o*]perylenes (VII) and (VIII) respectively.

[3] Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, 1953, p. 686.
[4] Wittig and Pieper, *Ber.*, 1940, **73**, 295; Wittig, *Annalen*, 1941, **546**, 142, 172; 1947, **558**, 201, 218.
[5] Miller and Mayo, *J. Amer. Chem. Soc.*, 1956, **78**, 1017; Mayo and Miller, *ibid.*, p. 1023.

The presence of one carbonyl group in compound (V) was ascertained by its reaction with phenylmagnesium bromide and lithium aluminium hydride, followed by hydrolysis in the usual manner, whereby the alcohol (VI) and 9′ : 10′-dihydro-10-9′-anthrylidenethiaxanthen (IX) respectively were formed.

Experimental

9-9′-*Fluorenylideneanthrone* (I).—A powdered mixture of 9 : 9-dichlorofluorene [6] (6 g.) and anthrone (5·4 g.) [7] was heated in a Pyrex glass tube (2·5 cm. diam.) in an ethyl phthalate bath. At 140° (bath-temperature) the solid began to melt and brisk evolution of hydrogen chloride occurred. The temperature was raised to about 160° for 2 hr., evolution of the gas nearly ceasing and the mass solidifying. The cooled mass was extracted with boiling xylene (20 c.c.), the filtrate cooled, and the yellowish-green solid was filtered off, triturated with ether, and dried (4 g.). From xylene–butanol it formed brownish-green crystals, m. p. 283—284° (deep violet melt), giving a deep green colour with concentrated sulphuric acid, moderately soluble in benzene, toluene, and xylene, sparingly soluble in methyl and ethyl alcohol, to deep violet solutions. This *product* (I) shows reversible and pronounced thermochromic effects in very dilute solutions, *e.g.*, benzene (deep violet ⟶ violet red, with fading). When pressed strongly with a glass pestle the crystals attained a permanent deep violet colour which changed back to brownish-yellow in presence of ether vapour (Found: C, 90·5; H, 4·6. $C_{27}H_{16}O$ requires C, 91·0; H, 4·5%).

9′ : 10′-*Dihydro*-10′-*hydroxy*-10′-*phenyl*-10-9′-*anthrylidenethiaxanthen* (VI).—To a solution of phenylmagnesium bromide (magnesium, 0·73 g.; bromobenzene, 4·7 g.; dry ether, 20 c.c.), dry benzene (100 c.c.) was added and the mixture treated gradually with powdered 10-9′-anthronylidenethiaxanthen [2] (V) (3·9 g.). The mixture was refluxed (with stirring) for 4 hr., the ether being allowed to evaporate slowly; it assumed a deep red-violet colour. The cooled mixture was poured into ice-cold water acidified with hydrochloric acid. The solid (A) which separated was filtered off, and the benzene layer separated, washed, and evaporated. The residue was added to (A) and the whole material (4 g.) crystallised from toluene–light petroleum (b. p. 80—100°) as pale green prismatic needles, m. p. 280—281° (deep brown melt). This *compound* gave a reddish-brown colour with concentrated sulphuric acid, and was moderately soluble in benzene, toluene, and xylene, slightly soluble in ethyl alcohol (Found: C, 85·0; H, 4·8; S, 6·5. $C_{33}H_{22}OS$ requires C, 85·0; H, 4·7; S, 6·9%).

9′ : 10′-*Dihydro*-10-9′-*anthrylidenethiaxanthen* (IX).—To pulverised lithium aluminium hydride (0·5 g.) was added dry ether (50 c.c.); stirring produced a milky suspension. After 15 min., the compound (V) (1 g.) in dry benzene (50 c.c.) was added gradually. The mixture was refluxed (with stirring) for 3 hr. and set aside overnight, then poured into ice-cold water acidified with hydrochloric acid, the solid (A) was filtered off, and the benzene layer separated, washed, dried, and evaporated. The residue was added to (A) and the whole *product* (0·65 g.) crystallised from toluene in fine prismatic needles, m. p. 306—308°, soluble in methyl and ethyl alcohols (Found: C, 86·5; H, 4·9; S, 8·6. $C_{27}H_{18}S$ requires C, 86·6; H, 4·8; S, 8·6%).

Photochemical Experiments.—The following experiments were carried in Pyrex glass tubes (2·5 cm. diam.). The benzene used was thiophen-free and dried over sodium.

(a) 9-9′-*Fluorenylideneanthrone* (I).—The compound (1·15 g.) suspended in benzene (70 c.c.) (violet solution) was placed in direct sunlight ($CaCl_2$ guard-tube) for one month (April); a pale yellow solution was produced. It was concentrated to about 7 c.c., then cooled and the straw-yellow crystals were filtered off (0·3 g.). They crystallised from glacial acetic acid in pale yellow long needles, m. p. 285°, not depressed by admixture with anthraquinone. The original mother-liquor was subjected to several fractional crystallisations, till its volume was about 1 c.c. The different crops of crystals separated proved to be anthraquinone (total 0·5 g.). The residual orange mother-liquor was freed from benzene and the residual oil (0·45 g.) was distilled under a vacuum. The yellow distillate crystallised from benzene–light petroleum (b. p. 60—80°) in pale yellow needles, m. p. 84°, not depressed by admixture with fluorenone. The Table indicates the acceleration of oxygen absorption with time. After illumination in the dark or in carbon dioxide in presence of sunlight, no colour change occurred and the original material was recovered unchanged.

[6] Smedley, *J.*, 1905, 1249.
[7] Meyer, *Org. Synth.*, Coll. Vol. I, 1944, p. 60.

Time (hr.)	1	2	3	4	5	6	9	11
Δp (cm.)	0	0	0	0·1	0·3	0·6	2·0	3·6
Time (hr.)	11·5	12·0	13·0	14·0	14·5	15·0	16·0	17·0
Δp (cm.)	4·2	5·0	5·5	6·2	6·3	6·3	6·3	6·3

(b) 10-9′-*Thiaxanthylideneanthrone* (V). (i) The compound (1 g.), suspended in benzene (25 c.c.), sealed under carbon dioxide, was left in direct sunlight for 2 weeks (October); the solution became reddish-brown with a deep fluorescence, and on concentration to about 5 c.c. under reduced pressure afforded 16-*oxo*-7-*thiadibenzo*[a, o]*perylene* (VII) (0·8 g.); this crystallised from benzene in orange-red prismatic needles, m. p. 245° (Found: C, 83·8; H, 3·4; S, 8·2. $C_{27}H_{14}OS$ requires C, 83·9; H, 3·6; S, 8·3%), giving an intense green colour with concentrated sulphuric acid, sparingly soluble in cold or hot ethyl alcohol with an orange-red colour and a yellow fluorescence (more intense in the cold). It dissolved in cold benzene, toluene, or xylene with a deep yellowish-green fluorescence. When a drop of the benzene solution was put on a glazed white porcelain plate, it looked bright yellow without any red colour, but dried to orange-red crystals.

(ii) Experiment (a) was repeated with 0·2 g. suspended in benzene (20 c.c.) under a calcium chloride guard-tube. Irradiation was for one week (October). The reddish-brown solution obtained was concentrated and the crystalline product formed was filtered off (0·12 g.) and identified as (VII).

(c) 9′ : 10′-*Dihydro*-10′-*hydroxy*-10′-*phenyl*-10-9′-*anthrylidenethiaxanthen* (VI). (i) This compound (1 g.), suspended in benzene (50 c.c.), sealed under carbon dioxide, was left in direct sunlight for 12 days (October); the solution became green with a yellow fluorescence, and on concentration to about 5 c.c. under reduced pressure and cooling, afforded crystals of 16-*hydroxy*-16-*phenyl*-7-*thiadibenzo*[a, o]*perylene* (VIII) (0·7 g.); this crystallised from benzene–light petroleum (b. p. 60—80°) in orange crystals, m. p. 275°. It is moderately soluble in benzene, toluene, and xylene, sparingly soluble in ethyl alcohol (Found: C, 85·0; H, 4·4; S, 6·3. $C_{33}H_{20}OS$ requires C, 85·4; H, 4·3; S, 6·9%).

(ii) Experiment (i) was repeated with 0·2 g. in 20 c.c. of benzene under a calcium chloride guard-tube, irradiation being for 5 days (October). The green solution obtained was concentrated and the crystalline product obtained was filtered off (0·1 g.) and identified as (VIII).

FACULTY OF SCIENCE, ALEXANDRIA UNIVERSITY,
ALEXANDRIA, EGYPT.

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675. *Oxazole Cyanine and* mero*Cyanine Dyes, and Intermediates. Part II.* Intermediates Derived from Desylamines* (1 : 2-*Diaryl*-2-*oxoethylamines*).

By R. A. JEFFREYS.

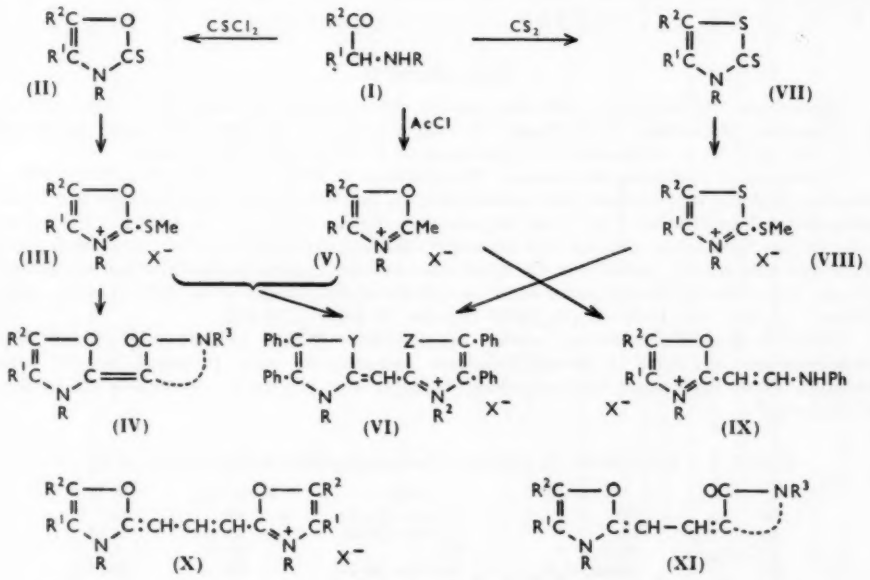
N-Alkyl- and *N*-aryl-desylamines (I) react with thiocarbonyl chloride, carbon disulphide, or acetyl chloride to give 4 : 5-diaryl-2-thio-oxazolines (II), 4 : 5-diaryl-2-thiothiazolines (VII), and 4 : 5-diaryl-2-methyloxazolium salts (V) respectively. These intermediates are used in the syntheses of mono- and tri-methincyanine dyes and *mero*cyanine dyes derived from oxazole and thiazole. Many of the dyes with short resonance paths are fluorescent and almost colourless.

CONTINUING the investigation of oxazole dyes and intermediates as photographically useful compounds, we wished to prepare a series of hitherto unknown monomethin oxazole cyanines (VI; Y = Z = O) and of *mero*cyanines (IV) with directly linked nuclei. The reaction between two equivalents of 2-methylazolium salt and pentyl nitrite in acetic anhydride, which provides symmetrical monomethincyanines in the benzoxazole series,[1] failed to give the required dyes in the oxazole series. An alternative synthesis was explored, involving the use of 2-alkylthio-oxazolium salts (III), which are intermediates common

* Oxazole Cyanine and *mero*Cyanine Dyes, and Intermediates, *J.*, 1952, 4823, is regarded as Part I.

[1] Fisher and Hamer, *J.*, 1934, 962.

to the preparation of dyes (IV) and (VI). The starting materials for the preparation of 4 : 5-diaryloxazole dyes, the desylamines (1 : 2-diaryl-2-oxoethylamines) (I), are readily available by the condensation of benzoins with amines in the presence of acid catalysts.[2] McCombie and Parkes[3] showed that *N*-phenyldesylamine with carbonyl chloride gives 3 : 4 : 5-triphenyloxazol-2-one, and we now find that desylamines and thiocarbonyl chloride give 4 : 5-diaryl-2-thio-oxazolines (II) with alkyl or aryl groups in the 3-position. These thiones condense on fusion with alkyl esters to form water-soluble 2-alkylthio-oxazolium salts (III). The intermediates (II) and (III) have recently been described by Gompper,[4] who prepared the 2-thio-oxazolines from oxazol-2-ones and phosphorus pentasulphide. The salts (III) react with 2-methyloxazolium salts (V), to give di-(3 : 4 : 5-substituted 2-oxazole)methincyanines (VI; Y = Z = O), and with ketomethylene heterocyclic compounds to give *mero*cyanines (IV). Both of these groups of dyes absorb strongly in the near-ultraviolet region and are almost colourless. Some are strongly fluorescent, as solids and in solution, especially in ultraviolet light. Compared with analogous cyanines derived from benzoxazole, naphth(1′ : 2′-4 : 5)oxazole, and naphth(2′ : 1′-4 : 5)oxazole, which have absorption maxima in methanol at 370, 400, and 395 mμ respectively, the 4 : 5-diphenyloxazole cyanines absorb at about 385 mμ, sometimes with inflections on the longer-wavelength side, at about 395 mμ. The crude desylamine from 4-methoxybenzoin and ethylamine was converted into the isomers 3-ethyl-4(or 5)-*p*-methoxyphenyl-5(or 4)-phenyl-2-thio-oxazoline (II; R = Et, R^1 = *p*-MeO·C_6H_4 or Ph, R^2 = Ph or *p*-MeO·C_6H_4), which were separated by chromatography. These were converted into isomeric dyes.



Desylamines also react with carbon disulphide, the products being the analogous 2-thiothiazolines (VII). These are also converted into useful dye intermediates (VIII) by fusion with alkyl esters, thus providing a new route to thiazole analogues of dyes (IV) and (VI). Unsymmetrical cyanines with one oxazole and one thiazole nucleus can also be

[2] Lutz, Freek, and Murphey, *J. Amer. Chem. Soc.*, 1948, **70**, 2015; Lutz and Murphey, *ibid.*, 1949, **71**, 478.
[3] McCombie and Parkes, *J.*, 1912, **101**, 1991.
[4] Gompper, *Chem. Ber.*, 1956, **89**, 1762.

obtained, with absorption maxima in methanol at *ca.* 415 mμ, *i.e.*, between those of the analogous oxazole and thiazole (440 mμ) cyanines. The thiazole dyes are also fluorescent.

Desylamines also condense with acetyl chloride in acetic anhydride to give 2-methyloxazolium salts (V) directly. Alternative methods [5] involve the isolation and subsequent quaternization of oxazole bases. The variety of desylamines available makes possible the synthesis of oxazolium salts and dyes possessing long-chain alkyl groups and aryl groups in the 3-position. Examples of 2-2′-anilinovinyl-4 : 5-diaryloxazolium salts (IX), symmetrical trimethincyanines (X), and dimethin*mero*cyanines (XI) have been prepared *via* 2-methyloxazolium salts (V) by previous procedures [5] or their modifications. 2-2′-Acetanilidovinyl derivatives of oxazoles are not readily prepared by refluxing anilinovinyl intermediates in acetic anhydride, and in dye syntheses that require acetanilidovinyl compounds this difficulty was overcome by using anilinovinyl compounds (1 mol.) with acetic anhydride (1 mol.) and triethylamine (1 mol. in excess of the usual quantity) in ethanol. Under these conditions, acetanilidovinyl derivatives could not be isolated, although good yields of dyes were obtained.

The vinylogous shifts of absorption maxima in methanol on passing from monomethin- to trimethin-oxazole and -thiazole dyes are 120 mμ and 140 mμ respectively, values in agreement with those found in other cyanine dye series (such as the benzazoles) in which the monomethin dyes have planar resonance systems: also, an increase in molecular extinction coefficient is observed on increasing the polymethin chain length.

Many of the dyes are strong sensitizers for photographic gelatino-silver halide emulsions, although dyes with long-chain alkyl substituents are less efficient sensitizers.

Experimental

Throughout the Tables the following solvent abbreviations are used: A = ethyl acetate, B = benzene, D = ether, E = ethanol, G = ligroin (b. p. 70—90°), L = light petroleum (b. p. 60—80°), M = methanol, N = nitrobenzene, P = pyridine, W = water.

Ethyl-(2-oxo-1 : 2-diphenylethyl)amine Hydrochloride (I,HCl; R = Et, $R^1 = R^2 = Ph$).—Benzoin (21·2 g.), 70% aqueous ethylamine (30 c.c.), and ethylamine hydrochloride (1 g.) were refluxed for 4 hr. After 2 hr., more aqueous ethylamine (15 c.c.) was added. The cooled solution was then made alkaline with aqueous N-sodium carbonate and extracted with ether. Hydrogen chloride was passed into the dried ether extract, and the precipitated *salt* was filtered off and recrystallized from ethanol–ether as a fluffy white powder, m. p. 236° (13·5 g., 49%) (Found: N, 5·1; Cl, 12·9. $C_{16}H_{18}ONCl$ requires N, 5·0; Cl, 12·8%).

Methyl-(2-oxo-1 : 2-diphenylethyl)amine hydrochloride (Table 1) and *ethyl-[1(and 2)-p-methoxyphenyl-2-oxo-2(and 1)-phenylethyl]amine hydrochloride* were prepared by the same method. Other desylamine hydrochlorides (Table 1) were prepared according to the method of Lutz *et al.*[2]

Table 1. *Desylamine (1 : 2-diaryl-2-oxoethylamine) hydrochlorides* (I,HCl).

R	$R^1 = R^2$	Form [a]	Yield (%)	M. p.
Me	Ph	Powder (E–D)	43	240° [a]
Bu	Ph	Powder (E–D)	33	229 [b]
n-$C_{16}H_{37}$	Ph [c]	Wax	90	—
Bu	p-MeO·C_6H_4	Needles (M–D)	68	204 [d]
n-$C_{18}H_{35}$	p-MeO·C_6H_4 [c]	Wax	64	—

[a] Goodson and Moffett, *J. Amer. Chem. Soc.*, 1949, **71**, 3219, report m. p. 216—220°. [b] Lutz, Freek, and Murphey, *J. Amer. Chem. Soc.*, 1948, **70**, 2015, report m. p. 184—186°. [c] Crude product used to prepare 2-methyloxazolium salt. [d] Found: N, 3·7; Cl, 9·8. $C_{26}H_{28}O_3NCl$ requires N, 3·8; Cl, 9·8%. [e] Solvent in parentheses.

4 : 5-*Diaryl-2-thio-oxazolines* (II) (Table 2).—A solution of the 1 : 2-diaryl-2-oxoethylamine hydrochloride (0·1 mol.) in water (125 c.c.) was made alkaline with sodium carbonate solution,

[5] Jeffreys, *J.*, 1952, 4823.

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TABLE 2. 4 : 5-*Diaryl-2-thio-oxazolines* (II).

R	R¹	R²	Form [a]	Yield (%)	M. p.	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
Et	Ph	Ph	Prisms (M)	53	163°	$C_{17}H_{15}ONS$	5·0	11·3	5·0	11·4
Bu	Ph	Ph	Needles (G)	20	145	$C_{19}H_{19}ONS$	4·3	10·2	4·5	10·4
n-C_6H_{17}	Ph	Ph	—	90		Oil; crude product used for dye preps.				
Ph	Ph	Ph	Prisms (N–E)	48	226 [a]	—	—	—	—	—
Et	*p*-MeO·C_6H_4	Ph	Needles } (B–L)	32 [b]	180	$C_{18}H_{17}O_2NS$	4·5	10·5	4·5	10·3
Et	Ph	*p*-MeO·C_6H_4	Cubes } (B–L)		145	$C_{18}H_{17}O_2NS$	4·5	10·5	4·5	10·3

[a] Gompper, *Chem. Ber.*, 1956, **89**, 1762, reports m. p. 229°. [b] Total crude yield. The isomers were separated by chromatography on alumina with ligroin–benzene mixtures as eluants. [c] Solvent in parentheses.

TABLE 3. 4 : 5-*Diaryl-2-methyloxazolium salts* (V).

R	R¹ = R²	X	Form [b]	Yield (%)	M. p.	Formula	Found (%) N	Found (%) Hal	Reqd. (%) N	Reqd. (%) Hal
Me	Ph	ClO_4	Plates (E–D)	46	156°	$C_{17}H_{16}O_6NCl$	—	10·3	—	10·2
Et	Ph	ClO_4	Leaflets (M–D)	62	152	$C_{18}H_{18}O_6NCl$	3·8	10·0	3·9	9·8
Bu	Ph	I	Needles (E–D)	77	179	$C_{20}H_{22}ONI$	3·2	31·0	3·3	30·3
n-C_8H_{17}	Ph	I	Leaflets (M–D)	63	130	$C_{24}H_{30}ONI$	2·7	27·5	2·9	26·7
n-$C_{12}H_{25}$	Ph	ClO_4	Wax [a]	—	—	—	—	—	—	—
n-$C_{16}H_{37}$	Ph	ClO_4	Wax [a]	—	—	—	—	—	—	—
Ph	Ph	I	Needles (M–D)	60	266	$C_{22}H_{16}ONI$	3·2	29·3	3·2	28·9
Bu	*p*-MeO·C_6H_4	ClO_4	Needles (M–D)	83	181	$C_{23}H_{24}O_7NCl$	3·1	8·0	3·1	7·9
n-$C_{12}H_{25}$	*p*-MeO·C_6H_4	ClO_4	Wax (A–G)	85	120	$C_{30}H_{42}O_7NCl$	2·6	6·5	2·5	6·3

[a] Crude product used to prepare 2-2′-anilinovinyl derivative. [b] Solvent in parentheses.

TABLE 4. *Monomethincyanine dyes* (VI).

R	R²	X	Form [b]	Yield (%)	M. p.	$\lambda_{max.}$ (mμ, MeOH)	$10^{-4}\varepsilon$	Formula	Found (%) N	Found (%) Hal	Reqd. (%) N	Reqd. (%) Hal
(a) *Di-*(3-*R*-4 :5 *-diphenyl-2-oxazole*)*methincyanine salts* (VI; R = R², Y = Z = O).												
Et	Et	ClO_4	Primrose leaflets (PM–D)	15	281° [a]	381	3·7	$C_{35}H_{31}O_6N_2Cl$	4·5	5·9	4·6	5·8
n-C_8H_{17}	*n*-C_8H_{17}	ClO_4	Cream leaflets (M–D)	21	184	385	3·8	$C_{47}H_{55}O_6N_2Cl$	3·6	4·6	3·6	4·6
						i 395						
Ph	Ph	I	Lemon-yellow (P–D)	30	>330	383	3·5	$C_{43}H_{31}O_2N_2I$	3·8	17·1	3·8	17·3
						i 392						
(b) [3-*R*-4 : 5-*diphenyl-2-oxazole*][3-*R*²-4 : 5-*diphenyl-2-thiazole*]*methincyanine salts* (VI; Y = O, Z = S).												
Et	Et	I	Amber plates (E–D)	21	273	420	6·4	$C_{35}H_{31}ON_2IS$	— [c]	19·6	—	19·5
Et	Bu	ClO_4	Lemon-yellow leaflets (P–D)	24	254	412	5·9	$C_{37}H_{35}O_5N_2ClS$	4·3	5·3	4·3	5·4
(c) [3-*R*-4 : 5-*diphenyl-2-thiazole*][3-*R*²-4 : 5-*diphenyl-2-thiazole*]*methincyanine salts* (VI; Y = Z = S).												
Et	Bu	ClO_4	Yellow needles (P–M)	33	279 [a]	438	6·7	$C_{37}H_{35}O_4N_2ClS$	4·1	—	4·2	—

[a] Decomp. [b] Solvent in parentheses. [c] Found : S, 5·0. Reqd. : S, 4·9%.

TABLE 5. *Symmetrical trimethincyanine dyes : di-*[3-*R*-4 : 5-*diaryl-2-oxazole*]*trimethincyanine salts* (X).

R	R¹ = R²	X	Form [a]	Yield (%)	M. p.	$\lambda_{max.}$ (mμ, MeOH)	$10^{-4}\varepsilon$	Formula	Found (%) N	Found (%) Hal	Reqd. (%) N	Reqd. (%) Hal
Bu	*p*-MeO·C_6H_4	ClO_4	Orange leaflets (M–D)	67	203°	512	8·1	$C_{45}H_{49}O_{10}N_2Cl$	3·3	4·5	3·4	4·4
						i 494						
n-C_8H_{17}	Ph	I	Orange Sponge (M–D)	75	219	505	9·5	$C_{49}H_{57}O_2N_2I$	3·4	15·6	3·4	15·3
						i 486						
Ph	Ph	I	Brick-red (M–D)	50	301	511	9·3	$C_{45}H_{43}O_2N_2I$	3·7	16·7	3·7	16·7
						i 492						

[a] Solvent in parentheses.

TABLE 6. 2-2′-*Anilinovinyl*-4 : 5-*diaryloxazolium salts* (IX). (*Prepared by the procedure used previously.*[5])

R	R¹ = R²	X	Form [a]	Yield (%)	M. p.	Formula	Found (%) N	Found (%) Hal	Reqd. (%) N	Reqd. (%) Hal
n-C_8H_{17}	Ph	I	Yellow (M–D)	87	182°	$C_{31}H_{36}ON_2I$	4·7	22·8 [c]	4·8	22·0
n-$C_{13}H_{25}$	Ph	ClO_4	,, (A–L)	69	127	$C_{36}H_{43}O_5N_2Cl$	4·6	5·9	4·6	5·8
n-$C_{13}H_{27}$	Ph	ClO_4	,, (M–D)	62	131	$C_{41}H_{55}O_5N_2Cl$	4·0	5·3	4·1	5·1
Ph	Ph	I	Orange-red (M–D)	62	260	$C_{29}H_{22}ON_2I$	5·1	23·4	5·2	23·4
Bu	*p*-MeO·C_6H_4	ClO_4	Yellow (E–D)	88	224	$C_{29}H_{31}O_7N_2Cl$	5·0	6·6	5·1	6·4
n-$C_{13}H_{25}$	*p*-MeO·C_6H_4	ClO_4	Orange (M)	54	169	$C_{37}H_{47}O_7N_2Cl$	4·1	5·5	4·2	5·3

[a] Solvent in parentheses. [b] Prisms; others are leaflets. [c] Found: C, 64·2; H, 6·2. Reqd.: C, 64·4; H, 6·1%.

TABLE 7. mero*Cyanines*: 3-*Alkyl*-5-(3-*R*-4 : 5-*diaryloxazolin*-2-*ylidene*)-2-*thio*-*azolid*-4-*ones* (IV).

R	R¹ = R²	R³	Form [d]	Yield (%)	M. p.	$\lambda_{max.}$ (mμ, MeOH)	$10^{-4}\varepsilon$	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
From 3-R³-2-*thiothiazolid*-4-*one*.												
Et	Ph	Et	(B–L)	64	179°	405	4·1	$C_{22}H_{20}O_3N_2S_2$	6·7	15·8	6·9	15·7
						420	4·2					
Et	Ph	$CH_2{\cdot}CO_2H$	Needles (B–L)	30	257	404	3·6	$C_{22}H_{16}O_4N_2S_2$	6·7	14·9	6·4	14·6
						417	3·5					
Bu	Ph	$CH_2{\cdot}CO_2Et$	Needles (B–L)	28	139	404	3·5	$C_{26}H_{26}O_4N_2S_2$	5·5	13·0	5·7	13·0
						416	3·4					
n-C_8H_{17}	Ph	Et	Powder (E)	49	106	408	4·4	$C_{28}H_{32}O_2N_2S_2$	5·7	13·0	5·7	13·0
Ph	Ph	$CH_2{\cdot}CO_2Et$	Leaflets (P–M)	74	331	404	—	$C_{28}H_{22}O_4N_2S_2$	5·5	12·6	5·5	12·5
						413	—					
Et	*b*	$CH_2{\cdot}CO_2H$	Powder (P–L)	42	250 [e]	411	—	$C_{23}H_{20}O_5N_2S_2$	6·0	13·9	6·0	13·7
Et	*b*	Et	(B–L)	—	180	415	—	}				
Et	*c*	Et	Prisms (B–L)	37	205	405	4·4	$C_{23}H_{22}O_3N_2S_2$	6·4	14·6	6·4	14·6
						419	4·3	}				
From 3-*ethyl*-2-*thio*-*oxazolid*-4-*one*.												
Et	Ph	Et	Needles (B–L) [e]	31	177	381	3·9	$C_{22}H_{20}O_2N_2S$	7·0	8·1	7·1	8·2
						395	3·3					
From 1 : 3-*diethyl*-2-*thiohydantoin*.												
Et	Ph	Et	Needles (G)	14	182	393	3·8	$C_{24}H_{24}O_2N_2S$	9·9	8·8	10·0	7·6

[a] Decomp. [b] R¹ = Ph, R² = *p*-MeO·C_6H_4. [c] R¹ = *p*-MeO·C_6H_4; R² = Ph. [d] Solvent in parentheses. [e] Cream-coloured; others are yellow.

TABLE 8. *Dimethin*mero*cyanines*: 3-*alkyl*-5-(3-*R*-4 : 5-*diaryl*-*oxazolin*-2-*ylidene*-*ethylidene*)-2-*thio*-*azolid*-4-*ones* (XI).

R	R¹ = R²	R³	Form [a]	Yield (%)	M. p.	$\lambda_{max.}$ (mμ, MeOH)	$10^{-4}\varepsilon$	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
From 3-R³-2-*thio*-*oxazolid*-4-*one*.												
Bu	*p*-MeO·C_6H_4	Et	Orange needles (B–L)	40	142°	495	7·5	$C_{28}H_{30}O_3N_2S$	5·2	6·2	5·5	6·3
Bu	Ph	Et	Red leaflets (B–L)	85	209	491	8·7	$C_{26}H_{26}O_2N_2S$	6·1	7·4	6·3	7·2
n-C_8H_{17}	Ph	Et	Orange needles (E–W)	68	103	491	8·8	$C_{30}H_{34}O_2N_2S$	5·5	6·7 [b]	5·6	6·4
Ph	Ph	Et	Red prisms (B–L)	56	250	491	8·7	$C_{28}H_{22}O_2N_2S$	6·0	—	6·0	—
From 1 : 3-*diethyl*-2-*thiohydantoin*.												
Bu	*p*-MeO·C_6H_4	Et	Red needles (B–L)	41	186	514	7·6	$C_{30}H_{32}O_4N_2S$	7·7	6·0	7·9	6·0
Ph	Ph	Et	Red powder (B–L)	73	247	511	8·6	$C_{30}H_{27}O_2N_2S$	8·5	6·8	8·5	6·5
n-C_8H_{17}	Ph	Et	Maroon needles (E–W)	87	140	513	9·5	$C_{32}H_{39}O_2N_2S$	7·6	[c]	7·9	—
From 3-R³-2-*thiothiazolid*-4-*one*.												
Ph	Ph	$CH_2{\cdot}CO_2Et$	Maroon leaflets (B–L)	35	244	512	9·6	$C_{30}H_{24}O_4N_2S_2$	5·2	12·0	5·2	11·9
						i 492						

[a] Solvent in parentheses. [b] Found: C, 71·5; H, 7·1. Reqd.: C, 71·7; H, 6·8.% [c] Found: C, 72·5; H, 7·5. Reqd.: C, 72·6; H, 7·4%.

and extracted with chloroform (600 c.c.). Thiocarbonyl chloride (0·1 mol.) was slowly added to the dried, stirred chloroform solution, cooled in ice-water. After 30 min. at room temperature the solution was washed thoroughly with sodium carbonate solution, and water. On removal of the chloroform from the dried solution, the product solidified, and was purified by recrystallization.

4 : 5-*Diaryl*-2-*methylthio-oxazolium Methyl Sulphates* (III; X = $MeSO_4$).—A 4 : 5-diaryl-2-thio-oxazoline (1 mol.) and methyl sulphate (1·5 mols.) were fused together on the steam-bath for ½—1 hr. The crude product, washed with ether, was used to prepare dyes.

3-*Ethyl*-4 : 5-*diphenyl*-2-*thiothiazoline* (VII; R = Et, $R^1 = R^2 = Ph$).—To a solution of ethyl-(2-oxo-1 : 2-diphenylethyl)amine hydrochloride (27·5 g., 0·1 mol.) and carbon disulphide (10 g., 0·13 mol.) in ethanol (100 c.c.) was added potassium hydroxide (11·2 g., 0·2 mol.) in water (12 c.c.), and the resulting solution was refluxed for 1 hr. The *product* was precipitated from the cooled solution with water, filtered off, and recrystallized from benzene–light petroleum as needles, m. p. 132° (17 g., 57%) (Found: S, 21·5. $C_{17}H_{15}NS_2$ requires S, 21·5%).

3-*Butyl*-4 : 5-*diphenyl*-2-*thiothiazoline* (VII; R = Bu, $R^1 = R^2 = Ph$) was prepared similarly, as glistening leaflets, m. p. 139° (from benzene–light petroleum), in 90% yield (Found: N, 4·2. $C_{19}H_{19}NS_2$ requires N, 4·3%).

3-*Alkyl*-2-*methylthio*-4 : 5-*diphenylthiazolium Toluene*-p-*sulphonates* (VIII; $R^1 = R^2 = Ph$, X = *p*-Me·C_6H_4·SO_3).—3-Alkyl-4 : 5-diphenyl-2-thiothiazoline (1 mol.) and methyl toluene-*p*-sulphonate (1·1 mols.) were fused together at 130° for 1 hr. The crude products, washed with ether, were used to prepare dyes.

4 : 5-*Diaryl*-2-*methyloxazolium Salts* (V) (Table 3).—A solution of the 1 : 2-diaryl-2-oxoethylamine hydrochloride (0·1 mol.) and acetyl chloride (0·1 mol.) in acetic anhydride (120 c.c.) was refluxed for 3 hr. Solvents were removed at the pump, and the residue was dissolved in a little ethanol. This solution was poured into aqueous sodium perchlorate or potassium iodide to precipitate the required salt, which was purified by recrystallization.

Monomethincyanine Dyes (VI) (Table 4).—4 : 5-Diaryl-2-methylthio-azolium salt (0·01 mol.), 4 : 5-diaryl-2-methylazolium salt (0·01 mol.), and triethylamine (0·01 mol.) in ethanol (20 c.c.) or pyridine (20 c.c.) were refluxed for 10 min. The cooled solution, if the dye did not crystallize, was poured into aqueous potassium iodide or sodium perchlorate to precipitate the *product*. The dye was recrystallized.

Symmetrical Oxazole Trimethincyanine Dyes (X) (Table 5).—4 : 5-Diaryl-2-methyloxazolium salt (0·01 mol.), 2-2′-anilinovinyl-4 : 5-diaryloxazolium salt (0·01 mol.) (see Table 6), acetic anhydride (0·01 mol.), triethylamine (0·02 mol.), and ethanol (20 c.c.) were refluxed together for ½—½ hr., and the solution was chilled; the *product* was filtered off and recrystallized.

3-*Alkyl*-5-(3-*R*-4 : 5-*diaryloxazolin*-2-*ylidene*)-2-*thio-azolid*-4-*ones* (IV) (Table 7).—4 : 5-Diaryl-2-methylthio-oxazolium salt (0·01 mol.), 3-alkyl-azolid-4-one (thiazolidone, oxazolidone, or hydantoin) (0·01 mol.), and triethylamine (0·01 mol.) in ethanol (25 c.c.) were refluxed for ¼ hr. A few drops of water were added, and the solution was chilled. The *dye* was filtered off, washed, and recrystallized.

3-*Alkyl*-5-(3-*R*-4 : 5-*diaryloxazolin*-2-*ylidene-ethylidene*)-2-*thio-azolid*-4-*ones* (XI) (Table 8).—2-2′-Anilinovinyl-4 : 5-diaryloxazolium salt (0·01 mol.), 3-alkyl-2-thio-azolid-4-one (as above) (0·01 mol.), acetic anhydride (0·01 mol.), and triethylamine (0·02 mol.) in ethanol (25 c.c.) were refluxed for 10 min. A few drops of water were added, and the solution was chilled. The *dye* was filtered off, washed, and recrystallized.

5-(3-*Butyl*-4 : 5-*diphenylthiazolin*-2-*ylidene*)-3-*carboxymethyl*-2-*thiothiazolid*-4-*one* (IV; thiazole analogue, R = Bu^n, $R^1 = R^2 = Ph$, $R^3 = CH_2$·CO_2H).—3-Butyl-2-methylthio-4 : 5-diphenylthiazolium toluene-*p*-sulphonate (2·6 g.), 3-carboxymethyl-2-thiothiazolid-4-one (1·0 g.) and triethylamine (0·5 g.) in ethanol (10 c.c.) were refluxed for 10 min. The chilled solution was filtered, and the *dye* recrystallized from pyridine–methanol as orange needles, m. p. 266° (decomp.) (0·9 g., 38%) (Found: S, 20·0. $C_{24}H_{22}O_3N_2S_3$ requires S, 19·9%), $\lambda_{max.}$ 423 mμ (ε 5·6 × 10^4 in MeOH).

[3-*Ethyl*-4-p-*methoxy*-5-*phenyl*-2-*oxazole*][3-*ethyl*-4 : 5-*diphenyl*-2-*oxazole*]*methincyanine Perchlorate* (Analogue of VI, Y = Z = O).—3-Ethyl-4-*p*-methoxyphenyl-2-methyl-5-phenyloxazolium toluene-*p*-sulphonate (4·65 g.), 3-ethyl-2-methylthio-4 : 5-diphenyloxazolium methyl sulphate (4·07 g.), and triethylamine (1·4 c.c.) in ethanol (20 c.c.) were refluxed for ¼ hr. Aqueous sodium perchlorate was added to the chilled solution, and the *dye* which precipitated was filtered off, washed with a little ethanol, and recrystallized from pyridine–water as cream leaflets, m. p.

[1] Solvent in parentheses. [2] Found: C, 71·5; H, 7·1. Reqd.: C, 71·7; H, 6·8%. [3] Found: C, 72·5; H, 7·5. Reqd.: C, 72·6; H, 7·4%.

XUM

277° (1·4 g., 22%) (Found: N, 4·3; Cl, 5·6. $C_{36}H_{33}O_7N_2Cl$ requires N, 4·4; Cl, 5·5%), $\lambda_{max.}$ 380 mμ (ε 3·9 × 10^4), infl. 394 mμ (cf. dyes in Table 4a).

The author is indebted to other members of these Laboratories as follows: to Dr. E. B. Knott for helpful discussion, to Messrs. V. Searle and V. Horton for absorption measurements and the preparation of intermediates respectively, and to Mr. C. B. Dennis for the microanalyses.

RESEARCH LABORATORIES, KODAK LIMITED,
WEALDSTONE, HARROW, MIDDLESEX.

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676. *Tracer Studies on Alcohols. Part II.* The Exchange of Oxygen-18 between* sec.*-Butyl Alcohol and Water.*

By C. A. BUNTON and D. R. LLEWELLYN.

The observation that, for a given perchloric acidity, the rate of racemisation of optically active *sec.*-butyl alcohol in water is twice the rate of oxygen exchange, has been extended to sulphuric acid solutions, and to higher acid concentrations than those used earlier. Plots of the logarithms of the first-order rate coefficients for racemisation and oxygen exchange against $-H_0$ (the Hammett acidity function) have slopes near to unity, indicating that the rate-determining step in both processes is the heterolysis of the oxonium ion, ROH_2^+. In the more concentrated acid solutions the rate of racemisation is less than twice the rate of oxygen exchange. This is because olefin elimination, which is negligible at low acid concentrations (Part I), increases with increasing acidity, and by subsequent hydration of the olefin provides an alternative route for oxygen exchange, with complete racemisation.

The stereochemistry of S_N1 reactions is discussed.

IN Part I * it was shown that over a range of perchloric acid concentrations (up to *ca.* M), the rate of oxygen exchange of *sec.*-butyl alcohol, followed isotopically, was, within experimental error, half the rate of racemisation of the optically active material, and that the oxygen exchange did not go by way of elimination and subsequent hydration of olefin. This result showed that every oxygen exchange between the alcohol and water gives complete inversion of configuration. The rates of exchange and racemisation were measured in aqueous acid, where the simpler mechanistic tests cannot be applied, but where a distinction between acid-catalysed uni- and bi-molecular processes can be made from the dependence of rate on acid concentration. Within the limited acidity range studied the rates of both racemisation and oxygen exchange followed the Hammett acidity function, and not the concentration of hydroxonium ions, $[H_3O^+]$. This distinction is diagnostic of mechanism because it can be shown that if the transition state of an acid-catalysed solvolytic reaction does not contain a water molecule from the solvent its rate should be proportional to h_0, but that the rate of a bimolecular reaction, where the transition state contains this water molecule, should be proportional, at least approximately, to the hydroxonium ion concentration, $[H_3O^+]$. These hypotheses have been tested in numerous examples where there is independent evidence.[1]

The kinetics of oxygen exchange at 99·8° were followed by the methods described in Part I. In some experiments isotopically enriched *sec.*-butyl alcohol was allowed to exchange its oxygen with isotopically normal water, and the increasing isotopic abundance of the water followed with time; in others the increase in the isotopic abundance of intially isotopically normal *sec.*-butyl alcohol in isotopically enriched water was followed by isolation of the alcohol. The racemisation was followed at 82·0° and 99·8°. The results

* The paper, *J.*, 1955, 604, is regarded as Part I.

[1] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, pp. 273—277; Long and his co-workers, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; *J. Phys. Chem.*, 1951, **55**, 829.

are shown in Fig. 1 and are tabulated. The Arrhenius activation energy for racemisation is *ca.* 36 kcal. mole^{-1}. This leads to a value of +12·3 cal. mole^{-1} deg.$^{-1}$ for the entropy of activation. A positive value for this term seems to be a characteristic of unimolecular acid-catalysed reactions.[2]

The slope of the logarithm of the rate coefficient for oxygen exchange against $-H_0$ is 1·02, and for racemisation is 0·97 (at both temperatures). At acid concentrations less than *ca.* 1·5 molal the rate of racemisation is almost exactly twice the rate of exchange, indicating that each exchange of oxygen atoms between alcohol and water gives complete inversion of configuration of the asymmetric carbon atom. The dependence of both exchange and racemisation on the Hammett function shows that water molecules from the solvent do not enter into the common slow stage of these processes (except by solvation of the ions concerned). This slow stage therefore is the formation of a carbonium ion intermediate whose life is not sufficiently long for the carbon atom to lose its asymmetry. This complete inversion for a unimolecular reaction is very similar to that observed in the acid hydrolysis of epoxides.[3]

FIG. 1. *Plots of the logarithms of the first-order rate coefficients* ($\times 10^5$) *for racemisation (upper line) and oxygen exchange (lower line) against* $-H_0$.

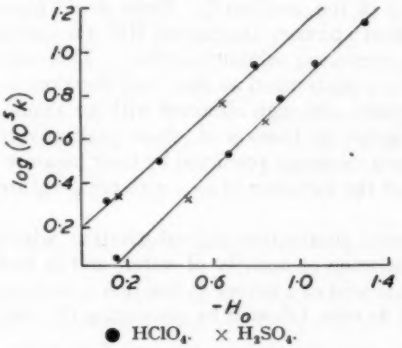
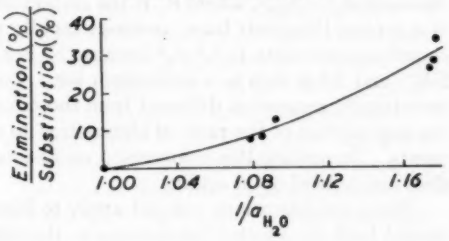


FIG. 2. *Dependence of elimination upon activity of water in perchloric acid.*



As the acidity is increased, and the water activity decreased, the elimination of olefin, which was insignificant at low acid concentrations (Part I), increases (see p. 3406). Elimination and subsequent hydration of the olefin will give a racemic alcohol (with no rearrangement [4]), and provided that allowance is made for the amount of oxygen exchange and racemisation by this route we find that oxygen exchange through substitution is giving complete inversion of configuration at each individual replacement, at all acidities up to 4m (see p. 3406).

This dependence of elimination upon acidity provides further evidence for the hypothesis that the processes studied are unimolecular in the rate-determining step. The stereochemical fate of a given carbonium ion is determined by competition between two reactions, one the capture of this ion to regenerate the alcohol with oxygen exchange, the other the loss of a proton to give an olefin, which will hydrate to regenerate the alcohol or can be aspirated out of solution. Thus the rate of oxygen exchange (in a closed system) will not depend on the fate of the carbonium ion. The formation of an olefin by loss of a proton from a carbonium ion does not require the immediate intervention of a water molecule. This follows from several independent pieces of evidence. The rate of hydration of an olefin follows the Hammett acidity function,[4, 5] and therefore does not require

[2] Long, personal communication.
[3] Long and Pritchard, *J. Amer. Chem. Soc.*, 1956, **78**, 2663, 2667.
[4] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 5372; Levy, Taft, and Hammett, *ibid.*, 1953, **75**, 1253.
[5] Taft, Purdie, Riesz, and De Fazio, *ibid.*, 1955, **77**, 1584.

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a water molecule in the slow step of reaction. This step is either the rearrangement of a π (or other) complex of the proton and olefin to a carbonium ion, or the addition to the olefin of a proton not closely bound to a water molecule.[6] Elimination of a proton from a carbonium ion should follow the same reaction path as the hydration and be independent of the concentration or activity of water. It is known that the rate of proton loss from the carbonium ion formed by *tert.*-butyl bromide in nitromethane, by the *E*1 mechanism, is not dependent on the presence of nucleophilic reagents such as halide ions.[6] In agreement with this is the observation that there is no deuterium isotope effect in the *E*1 elimination from a tertiary alkyl carbonium ion.[7]

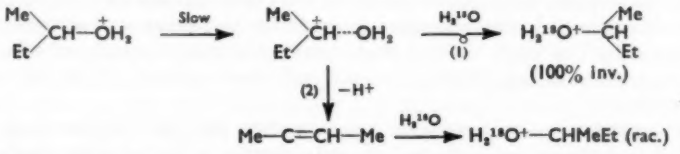
The ratio of elimination to substitution (with oxygen exchange) is given by the expression :

$$\frac{\text{Elimination (\%)}}{\text{Substitution (\%)}} \propto \frac{1}{a_{H_2O}} \cdot \frac{f_S^*}{f_E^*}$$

where f_S^* and f_E^* are the activity coefficients of S* and E*, the transition states for attack of a water molecule on, and elimination of a proton from, the carbonium ion. The transition state for substitution will contain a water molecule from the solvent, that for elimination will not. The ratio of elimination to substitution plotted against the reciprocal of the water activity, a_{H_2O}, does not give a straight line (Fig. 2), the ratio f_S^*/f_E^* increasing with increasing acidity (decreasing water activity of the medium [8]). Deno *et al.*[9] have shown that f_{R^+}/f_{HB^+}, where R^+ is the carbonium ion of a tertiary alcohol and HB^+ the cation of a typical Hammett base, increases rapidly with increasing sulphuric acidity. This ratio should approximate to f_S^*/f_E^* because S* is akin to a protonated alcohol, and therefore to HB^+, and E* is akin to a carbonium ion. Our results, although obtained with an alcohol structurally somewhat different from those investigated by Deno *et al.*, show qualitatively the dependence of the ratio of elimination to oxygen exchange predicted by their measurements. In making this comparison we assume that the variation of a_{H_2O} with temperature does not depend upon acidity.

These considerations will not apply to bimolecular elimination and substitution, which should both be affected by changes in the concentration or activity of water, and in fact proton loss from the β-carbon atom of the conjugate acid of a ketone (a reaction analogous to *E*2 elimination) requires a water molecule, and its rate, followed by measuring the rate of enolisation, is proportional to $[H_3O^+]$.[1]

Oxygen exchange and racemisation *via* substitution and elimination, with subsequent hydration, can therefore be represented as :



In this scheme the slow formation of the carbonium ion is the rate of oxygen exchange, and at low acidities (where elimination can be neglected) this is the rate of inversion of configuration of the carbonium ion, steps 1 and 2 being fast.

The solvent water molecule attacks the carbonium-ion centre sufficiently soon after the energy maximum is reached for the expelled water molecule to exert a marked " shielding " effect, giving complete inversion of configuration, but the kinetic form shows that making and breaking of these bonds are not synchronous. This means that the

[6] de la Mare, Hughes, Ingold, and Pocker, *J.*, 1954, 2930.
[7] Shiner, *J. Amer. Chem. Soc.*, 1953, **75**, 2925.
[8] Robinson and Baker, *Trans. Roy. Soc. New Zealand*, 1946, **76**, 250.
[9] Deno and his co-workers, *J. Amer. Chem. Soc.*, 1955, **77**, 3044; data reported at Sixth Reaction Mechanism Conference, Swarthmore College, 1956.

lifetime of the carbonium-ion intermediate, which is determined by the rates of water attack (1) and the proton loss (2), is not long enough for the expelled water molecule to move sufficiently far away to make the carbon atom, at the reaction centre, susceptible to attack from all directions. This will no longer be true when the carbonium ion is stabilised by aryl groups, and the acid-catalysed oxygen exchange of 4-methoxydiphenylmethanol gives complete loss of optical activity at every step of substitution.[10]

The Steric Course of S_N1 *Reactions.*—In 1937 it was shown that, in the absence of configuration-retaining groups, the product of an S_N1 reaction was usually partially racemic, with some inversion of configuration.[11] In some cases, particularly where kinetic distinctions are not clear-cut, it has been assumed that absence of complete racemisation is proof of a bimolecular component of mechanism. Much recent work has shown that this is not necessarily correct, although the converse, that observation of racemisation is evidence for a unimolecular mechanism, does hold.

Oxygen exchange between *sec.*-butyl alcohol and water is one of several reactions in which kinetic, or other, evidence shows that the transition state does not contain a solvent or reagent molecule, but in which the carbon centre is completely inverted.

The acid hydrolysis of epoxides is a unimolecular process,[3] but formation of the *trans*-diol shows that the carbon atom at the reaction centre is completely inverted. Similarly there are a large number of substitutions at the $C_{(1)}$ atom of a hexose ring, which are carried out under conditions in which an S_N1 reaction is expected, and which give complete inversion of the configuration of this atom.[12] Interpretation of the stereochemistry of many of these reactions is complicated by the presence of acetoxy-groups, which may interact with the carbonium-ion centre. However, recently it has been shown that the methanolysis of 2 : 3 : 4 : 6-tetra-*O*-methyl-α-D-glucopyranosyl chloride gives a completely inverted product.[13] This is a system in which there are no interfering groups.

In an intensive series of investigations on the hydrolysis of alkyl hydrogen sulphates, Burwell *et al.*[14] find almost complete inversion of configuration for the base-hydrolysis of optically active *sec.*-alkyl hydrogen sulphates. The rate of these reactions is little affected by hydroxide ion, is faster than those of the primary alkyl compounds, and is unaffected by steric hindrance. This evidence, and that from olefin formation, suggests that the mechanism is S_N1, although these reactions give little racemisation or rearrangement of the carbon skeleton for the simple *sec.*-alkyl compounds.

Methanolysis of 1-methylheptyl toluene-*p*-sulphonate gives a completely inverted product, at a rate little affected by added methoxide ion, and faster than that of the primary alkyl compounds.[15] This substitution is therefore similar to those of the alkyl hydrogen sulphates.

The only cases of S_N1 solvolyses giving complete racemisation are those in which the carbonium ion is stabilised by strongly electron-releasing groups, or in which the solvent molecules are such poor nucleophilic agents that the life of the carbonium ion is long compared with the rate of attack upon it. This conclusion does not seem to be particularly dependent on the nature of the leaving group.

Experimental

Experimental methods are in general those described in Part I. *sec.*-Butyl alcohol was resolved through the brucine salt of its hydrogen phthalate;[16] a specimen had b. p. 98—99°, $[\alpha]_D^{25}$ +6·86°.

[10] I. Wilson, unpublished results.
[11] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell & Sons, Ltd., London, 1953.
[12] Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 1; Haynes and Newth, *ibid.*, 1955, **10**, 207.
[13] Rhind-Tutt and Vernon, personal communication.
[14] Burwell *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1462; 1955, **77**, 6441.
[15] Bunton and Deschamps, unpublished results.
[16] Pickard and Kenyon, *J.*, 1911, **99**, 45; Kanter and Hauser, *J. Amer. Chem. Soc.*, 1953, **75**, 1744.

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Isotopically enriched *sec.*-butyl alcohol was that used as described in Part I. Its isotopic abundance in oxygen was 9·73 atom % excess.

Kinetics of racemisation were followed in aqueous perchloric and sulphuric acid at 82·0° and 99·8°. At appropriate times the optical activity of the solution was measured at 25°. Oxygen exchange was followed under conditions similar to those of racemisation but at 99·8° only. The first-order rate coefficients for oxygen exchange and racemisation were calculated as described in Part I. Some of the results shown in the Fig. 1 were calculated from data in Part I and the activation energy determined here.

Values of the acidity function were interpolated from published values, the effect of temperature differences and of the *sec.*-butyl alcohol being neglected.[17] The latter effect should not affect our general conclusions, although it may alter the slope of the plots of log k against $-H_0$.

Examples of kinetic runs are given below, k being obtained graphically.

Exchange of isotopically enriched sec.*-butyl alcohol with isotopically normal water at* 99·8°. $HClO_4$] = 4·10 molal. N is the abundance of ^{18}O in atom % excess.

Time (min.)	36	111	174	270	∞
N (water)	0·090	0·208	0·238	0·257	0·291 (calc.)

10^5k = 13·4 (sec.$^{-1}$)

Exchange of isotopically normal sec.*-butyl alcohol with isotopically enriched water (abundance = 0·641 atom % excess), at* 99·8°. [H_2SO_4] = 1·82 molal.

Time (min.)	100	190	250	305	∞
N (Bu^{s}OH)	0·071	0·126	0·147	0·190	0·619 (calc.)

10^5k = 2·07 (sec.$^{-1}$)

Racemisation of optically active sec.*-butyl alcohol at* 82·0°. [$HClO_4$] = 2·34 molal.

Time (hr.)	0	5·2	13·2	21·1	27·0	36·4	44·2	51·9
$[\alpha]_D^{28}$	1·100°	1·007°	0·815°	0·686°	0·603°	0·470°	0·393°	0·340°

10^6k = 6·30 (sec.$^{-1}$)

Rates of exchange and racemisation in aqueous acid.

Exchange runs.

At 99·8°	$HClO_4$ (m)					H_2SO_4 (m)	
[Acid]	1·152[a]	2·35[b]	2·94	3·40[b]	4·10[b]	1·82	2·52
10^5k (sec.$^{-1}$)	1·09	3·36	5·74	8·57	13·4	2·07	4·90

[a] From results in Part I. [b] *sec.*-Butyl alcohol initially enriched in ^{18}O.

Racemization runs.

At 99·8°	$HClO_4$ (m)			H_2SO_4 (m)		$HClO_4$ (m) at 82·0°	
[Acid]	1·096	1·484	2·57	1·085	2·10	1·45	2·34
10^5k (sec.$^{-1}$)	1·93	3·03	8·20	2·15	5·95	0·258	0·630

Formation of Olefin.—The olefin was swept out of solution in a stream of nitrogen, as fast as it was formed, and trapped at −80°. Its amount was determined by addition of a known excess of bromine in carbon tetrachloride and estimation of the residual bromine iodometrically.

The results of these experiments in aqueous perchloric acid at 99·8° are tabulated :

[$HClO_4$] (m)	1·79	1·86	2·04	3·12	3·15	
Time (hr.)	6	7	5·5	4·5	4·5	7
Olefin (%)	3·2	3·8	5·2	13·6	15	23
$\frac{\text{Elimination}}{\text{Exchange}}$ (%)	8·1	8·3	12	21	22	26

(The rates of exchange were interpolated.)

On the assumption that at all acidities exchange *via* substitution gives complete inversion of configuration and exchange *via* elimination and hydration gives a racemic alcohol we calculate, from the known amount of elimination, that for 3m-perchloric acid the ratio k_R/k_E should be

[17] Bartlett and McCollum, *ibid.*, 1956, **78**, 1441.

1·8 and the actual value is 1·85. With 2m-perchloric acid the observed and calculated ratios are 1·9.

The authors are indebted to Professors E. D. Hughes, F.R.S., C. K. Ingold, F.R.S., and F. A. Long for their valuable suggestions on this work, and to Mr. P. Chaffe for help with the isotope analyses.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON. [*Received, February 22nd,* 1957.]

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677. *Olefinic Additions with Asymmetric Reactants. Part IV.* The Addition of (±)-, (+)-, and (−)-1-Phenylpropane-2-thiol to Olefins. The Optical Stability of Asymmetric Sulphones.*

By C. L. ARCUS and P. A. HALLGARTEN.

Free-radical and Michael additions of (±)-, (+)-, and (−)-1-phenylpropane-2-thiol to β-nitrostyrene are described, together with separations of the diastereoisomeric sulphides or the corresponding sulphones. Reactions of the (±)-thiol with *trans*-1 : 2-dibenzoylethylene and 4′-nitrochalkone have been investigated.

The steric course of addition is discussed. (−)-2 : 4-Dinitrophenyl α-methylphenethyl sulphone is optically stable in acetic acid at 100°.

FOR a further study of dissymmetric olefinic addition, it appeared that an asymmetric thiol would be of use, it being known that thiols add readily to olefins of suitable structure by both a free-radical and an anionic (Michael) mechanism. A method for the preparation of (±)-, (+)-, and (−)-1-phenylpropane-2-thiol has been described.[1] The addition of this thiol (I) to an olefin (III) leads potentially to the diastereoisomeric sulphides (VI) and (VII) and if asymmetry in the thiol (I) results in dissymmetric addition (partial asymmetric synthesis), the sulphides will be formed in unequal amounts. In the present work a number of such additions have been investigated.

β-*Nitrostyrene.*—Addition of (±)-1-phenylpropane-2-thiol to β-nitrostyrene, whether initiated by ascaridole (a free-radical reaction) or catalysed by piperidine, yielded two diastereoisomers, (±)-α-methylphenethyl 2-nitro-1-phenylethyl sulphide-A and -B, which were separated by fractional crystallisation and with hydrogen peroxide in acetic acid gave the corresponding sulphones, -A and -B.

Ascaridole-initiated addition of the (+)-thiol (90% optically pure) gave an oil from which solid sulphides could not be obtained; oxidation, and fractional crystallisation of the product, yielded a (−)-sulphone-A and impure (+)-sulphone-B. A similar procedure with optically pure (−)-phenylpropane-2-thiol gave the diastereoisomeric sulphides as an oil, and thence a (+)-sulphone-A and (−)-sulphone-B. These two sulphones were also obtained by oxidation of the sulphides from the piperidine-catalysed addition of the (−)-thiol.

Addition of (±)-, (+)-, *and* (−)-1-*Phenylpropane-2-thiol to* β-*Nitrostyrene.*

Thiol	Sulphide-A	Sulphone-A	Sulphide B	Sulphone B
(±)-	$d_Dl_\alpha + l_Dd_\alpha$ M. p. 76°	$d_Dl_\alpha + l_Dd_\alpha$ M. p. 117·5°	$d_Dd_\alpha + l_Dl_\alpha$ M. p. 53°	$d_Dd_\alpha + l_Dl_\alpha$ M. p. 111°
(+)-	—	d_Dl_α. M. p. 140° $[\alpha]^{17}$ −46·5°	—	d_Dd_α. M. p. 79—83° * $[\alpha]^{21}$ +74·5°
(−)-	—	l_Dd_α. M. p. 139·5° $[\alpha]^{21}$ +46·5°	—	l_Dl_α. M. p. 102·5° $[\alpha]^{20}$ −89·5°

* Sterically impure. [α] are for λ 5893 Å and acetone solutions.

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* Part III, *J.*, 1955, 34.

[1] Arcus and Hallgarten, *J.*, 1956, 2937.

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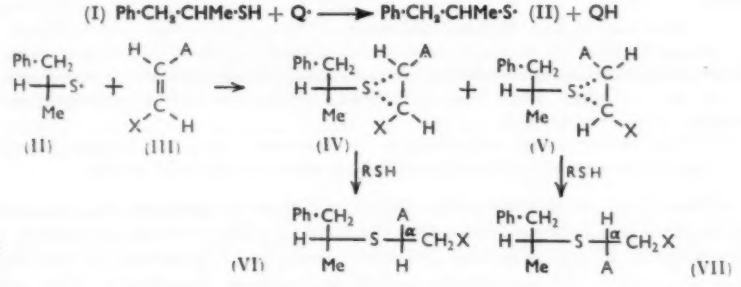
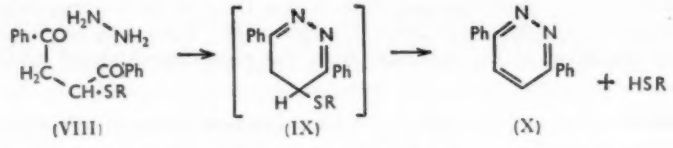
The piperidine-catalysed addition of five sterically symmetrical arenethiols to β-nitrostyrene was found by Cason and Wanser [2] to yield in each instance a single product. The product from thiophenol was shown to be 2-nitro-1-phenylethyl phenyl sulphide, by reduction to the amine which was also formed by reaction of β-chlorophenethylamine with sodium thiophenoxide. It is concluded that the present sulphides are the diastereoisomers of analogous structure, as given above.

(+)- and (−)-1-Phenylpropane-2-thiol are assigned the arbitrary configurations d_R and l_R (R referring to the α-methylphenethyl radical); the new asymmetric centre which is present in the sulphides and sulphones is termed d_α or l_α [cf. (VI) and (VII)]. The rotations for the sulphones derived from the (−)-thiol, given in the Table, show that the new centre (α) contributes a (+)-rotation in the A- and a (−)-rotation in the B-sulphone; the assignments, $l_R d_\alpha$, etc., in the Table follow from this correlation and from the fact that a 1 : 1 mixture of (+)- and (−)-sulphone-A gave a (±)-sulphone of m. p. 117—118°.



Quantitative determination of ratios of diastereoisomers did not prove practicable, but in every instance a substantial amount of each diastereoisomer was isolated, and it is proved that neither the peroxide-initiated free-radical addition nor the base-catalysed Michael addition proceeds unilaterally to yield the new asymmetric centre in a single configuration.

trans-1 : 2-*Dibenzoylethylene*.—Reaction, initiated by ascaridole, of (±)-1-phenylpropane-2-thiol with *trans*-1 : 2-dibenzoylethylene gave a crystalline sulphide, $CH_2Ph{\cdot}CHMe{\cdot}S{\cdot}CH(COPh){\cdot}CH_2{\cdot}COPh$, m. p. 87·5°, together with an oil probably containing a diastereoisomer. The oil, on reaction with hydrazine, formed a sulphur-containing material which on purification yielded 3 : 6-diphenylpyridazine (X); it is probable that the sulphide (VIII) gave a dihydropyridazyl sulphide (IX) which by



elimination formed the diphenylpyridazine. The oil is therefore considered to have contained a dibenzoylethyl α-methylphenethyl sulphide, although no information on its configuration was obtained from its conversion into diphenylpyridazine.

The sulphides (crystalline solid, and oil) were oxidised by hydrogen peroxide in cold acetic acid to the same sulphone. In this instance the sulphone contains a carbonyl group adjacent to the second asymmetric centre, and conversion into the most stable diastereoisomer is possible by enolisation. It is probable that, in addition to the crystalline

[2] Cason and Wanser, *J. Amer. Chem. Soc.*, 1951, **73**, 142.

isomer, a second diastereoisomeric sulphide is formed in the initial reaction, but definite proof is lacking.

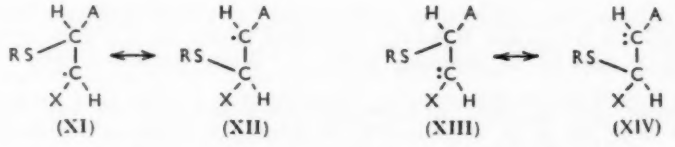
Oxidation of the sulphide (oily or crystalline) with hydrogen peroxide in hot acetic acid gave *trans*-1 : 2-dibenzoylethylene, no sulphone being obtained. Addition of toluene-ω-thiol to *trans*-1 : 2-dibenzoylethylene, initiated by ascaridole, gave benzyl 1 : 2-dibenzoylethyl sulphide, oxidised in the cold to the sulphone in good yield; but oxidation in hot acetic acid gave a reduced yield of sulphone together with *trans*-1 : 2-dibenzoylethylene.

(±)-1 : 2-Dibenzoylethyl α-methylphenethyl sulphide (m. p. 87·5°), benzyl 1 : 2-dibenzoylethyl sulphide, and the corresponding sulphones are stable in hot acetic acid; elimination of the sulphur-containing group is therefore an accompaniment of oxidation, and not a dissociation of the initial or final compound in the solvent.

Addition of toluene-ω-thiol to 4′-nitrochalkone, initiated by ascaridole, gave benzyl 2-*p*-nitrobenzoyl-1-phenylethyl sulphide. From the product of the similar addition of (±)-1-phenylpropane-2-thiol there was isolated a single (±)-α-methylphenethyl 2-*p*-nitrobenzoyl-1-phenylethyl sulphide, $CH_2Ph{\cdot}CHMe{\cdot}S{\cdot}CHPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4{\cdot}NO_2$, though the low yield made it uncertain whether this diastereoisomer is the major product.

(±)-1-Phenylpropane-2-thiol did not react with coumarin (ascaridole, piperidine), benzylideneindene (ascaridole), or *iso*phorone (ascaridole).

The probable course of peroxide-initiated addition is set out in (I–VII). Q· denotes a radical formed by decomposition of ascaridole; (IV) and (V) represent diastereoisomeric intermediate radicals; these are resonance hybrids: *e.g.*, (IV) represents the resonance hybrid of forms (XI) and (XII); the results are however adequately described if (IV) is replaced by (XI) only, since the intermediate reacts through this form in the final stage, when, also, $C_{(\beta)}$ becomes symmetrical.



Dissymmetric addition has been discussed with respect to carbonyl reactions by Reid and Turner,[3] and to olefins in Part I.[4] In the present reaction the rates of formation of the diastereoisomeric intermediates (IV) and (V) will, in principle, differ, and the rates of reaction of (IV) and (V) with the asymmetric thiol, leading to (VI) and (VII), will also be different. However, the latter stage has no effect on the steric structure of (VI) and (VII), whence this rate difference is not significant from the standpoint of dissymmetry. The yields of (VI) and (VII) reflect, therefore, the rates at which (IV) and (V) are formed; and since these yields do not differ widely, neither do these rates.

The course of the piperidine-catalysed Michael reaction is closely analogous to that for the free-radical addition; the thiol-anion from the first stage:

$$[CH_2]_5{>}NH + CH_2Ph{\cdot}CHMe{\cdot}SH \longrightarrow [CH_2]_5{>}NH_2^+ + CH_2Ph{\cdot}CHMe{\cdot}S^-$$

affords intermediates similar to (IV) and (V), and in the final stage the conjugate acid of the base gives up a proton, yielding (VI) and (VII), and regenerates the base. The resonance hybrid of (XIII) and (XIV) replaces that of (XI) and (XII) in the above arguments.

Configurations assigned to the oily sulphides depend on retention of configuration during oxidation of the thiols, by hydrogen peroxide in acetic acid, to the crystalline sulphones. The isolation of the active sulphones precludes facile inversion at the asymmetric centres,

[3] Reid and Turner, *J.*, 1949, 3365.
[4] Abbott and Arcus, *J.*, 1952, 1515.

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since this would lead to racemic products. But to provide a more direct test, (−)-2 : 4-dinitrophenyl α-methylphenethyl sulphone, containing a single asymmetric centre, was heated in dry acetic acid at 100°: the rotatory power of the solution did not alter appreciably during 8 hr., and the sulphone was recovered substantially unchanged. In relation to this it may be noted that, whereas α-phenylsulphonylpropionic acid racemises in N-hydrochloric acid at 25°,[5] probably *via* the enolic form of the carboxyl group, α-phenylsulphonylethanesulphonic acid is optically stable in this solvent at 100°.[6]

Experimental

M. p.s are corrected. Heating for addition reactions was in a thermoregulated oil-bath at 100°, and for oxidations on a steam-bath. Hydrogen peroxide was the 34% aqueous solution. Specific rotations were determined with acetone solutions at *l* 0·5.

Additions.—β-Nitrostyrene. The β-nitrostyrene–thiol mixtures were heated under nitrogen which had been deoxygenated by passage through Fieser's solution.

(i) (±)-*Thiol.* β-Nitrostyrene (2·38 g.) and (±)-1-phenylpropane-2-thiol (2·38 g.) were heated with ascaridole (1 drop) for 5 hr., then chilled to −80°; a glass was formed which on treatment with light petroleum (b. p. 40—60°) crystallised. Recrystallisation of the product (1·8 g.; m. p. 66—70°) from the same solvent yielded (±)-*α-methylphenethyl 2-nitro-1-phenylethyl sulphide-A* (1·2 g.), m. p. 73—76°, which on further crystallisation formed rhombs, m. p. 76° (Found: C, 67·95; H, 6·35; N, 4·85; S, 10·3. $C_{17}H_{19}O_2NS$ requires C, 67·75; H, 6·35; N, 4·65; S, 10·7%). Evaporation of the first filtrate gave an oil from which crystals (0·6 g.; m. p. 40·5—42·5°) separated. After recrystallisation from ethanol they (0·34 g.) had m. p. 49·5—51·5°, and yielded on further crystallisation (±)-*sulphide-B*, rectangular plates, m. p. 53·5° (Found: C, 67·7; H, 6·35; N, 4·5; S, 10·55%). From filtrates two further crops were obtained: 0·16 g., m. p. 72—74·5°; 0·13 g., m. p. 49·5—52·5°. The total yield of sulphides was 44%.

In other experiments, β-nitrostyrene (2·65 g.) and (±)-1-phenylpropane-2-thiol (2·65 g.) gave (±)-sulphide-A (1·1 g.) and -B (0·52 g.), and 0·38 g. of each reactant gave (±)-sulphide-A (0·33 g.) and -B (0·24 g.) (A separating slowly and nearly completely before B crystallised).

β-Nitrostyrene (2·17 g.) and (±)-1-phenylpropane-2-thiol (2·17 g.) were heated with piperidine (3 drops) for 4¼ hr. Chilling did not induce crystallisation but treatment with methanol gave a solid and from the solvent two further crops separated; the combined material (1·2 g.; m. p. 65—69°) was crystallised from ethanol: (±)-sulphide-A (0·61 g.), m. p. and mixed m. p. 74·5—76°, was obtained. The filtrates yielded (±)-sulphide-B (0·30 g.), m. p. and mixed m. p. 52·5° (total yield of sulphides 34%).

Except for the first small-scale separation, above, the aggregate yield of identified sulphides is much below 100%, whence ratios of diastereoisomers cannot be calculated with sufficient certainty. Further, with regard to both sulphides and sulphones, compounds of series A are the less soluble, and hence more likely to be isolated completely.

The (±)-sulphide-A (0·50 g.) was heated in acetic acid (6 ml.) for 5 min. with hydrogen peroxide (3 ml.). The whole was then frozen to −80° and allowed to warm to room temperature: a product (0·33 g.), m. p. 114—115°, was obtained. After three recrystallisations from ethanol it yielded (±)-*α-methylphenethyl 2-nitro-1-phenylethyl sulphone-A*, needles, m. p. 117·5° (Found: O, 19·35; S, 9·6. $C_{17}H_{19}O_4NS$ requires O, 19·2; S, 9·6%). Similar oxidation of (±)-sulphide-B (0·35 g.) gave a product (0·15 g.), m. p. 100—100·5°, which after two recrystallisations from ethanol yielded (±)-*sulphone-B*, needles, m. p. 111° (Found: S, 9·55%). In each of these oxidations further sulphone was obtained on dilution of filtrates with water, and in neither was β-nitrostyrene encountered.

(ii) (+)-*Thiol.* β-Nitrostyrene (3·12 g.) and (+)-1-phenylpropane-2-thiol (α^{17}_{5893} +6·08°; *l*, 0·5) (3·14 g.) were heated with ascaridole (2 drops) for 6 hr. The product did not crystallise at −80°, on treatment with ethanol, methanol, and light petroleum, or on refrigeration for 7 months. This material (5·6 g.) was oxidised as described for the (−)-thiol. The solid product

[5] Ramberg and Hedlund, *Arkiv Kemi, Min., Geol.*, 1938, **13**, *A*, No. 1, p. 11.
[6] Hedlund, *ibid.*, No. 12, p. 13.

(3·6 g.) was fractionally crystallised from ethanol; there were isolated (−)-*sulphone-A* (0·33 g.), needles, m. p. 140°, $[\alpha]_{5893}^{17}$ −46·5° (*c* 4·296) (Found: O, 19·25; S, 9·3%), and (+)-sulphone-B (not completely free from isomers; 0·12 g.), m. p. 79—83°, $[\alpha]_{5893}^{21}$ +74·6° (*c* 2·332).

(iii) (−)-*Thiol*. β-Nitrostyrene (5·33 g.) and (−)-1-phenylpropane-2-thiol (α_{5893}^{23} −13·46°; *l* 1·0) (5·33 g.) were heated with ascaridole (3 drops) for 6 hr. The product (which did not solidify) was heated in acetic acid (60 ml.) for 5 min. with hydrogen peroxide (40 ml.). The solution was chilled and poured into ice-cold water (1 l.). On fractional crystallisation from ethanol, it (7·6 g.) yielded (+)-*sulphone-A* (1·60 g.), needles, m. p. 139·5°, $[\alpha]_{5893}^{20}$ +47·0° (*c* 5·016) (Found: O, 19·0; S, 9·15%). The most soluble fraction, after draining on a porous plate, gave a solid (1·87 g.) of which three portions (total 1·19 g.) were subjected to vacuum-sublimation for 28 hr. β-Nitrostyrene (0·69 g.), m. p. 53·5—55·5° alone and when mixed with a specimen of m. p. 57°, sublimed; and there remained (−)-sulphone-B (0·33 g.), m. p. 100·5—102·5°, $[\alpha]_{5893}^{21}$ −89·1° (*c* 2·644).

β-Nitrostyrene and this thiol (each 4·39 g.) were heated with piperidine (4 drops) for 6½ hr. The resultant oil was oxidised as above and the product (6·0 g.) fractionally crystallised from ethanol. It yielded (+)-sulphone-A (1·57 g.), m. p. 140°, $[\alpha]_{5893}^{22}$ +46·0° (*c* 5·046), and (−) *sulphone-B* (0·12 g.), m. p. 102·5°, $[\alpha]_{5893}^{20}$ −89·5° (*c* 2·478) (Found: O, 18·75; S, 9·15%). These specimens, when mixed with the corresponding specimens from the peroxidic addition, had m. p.s 139·5° and 101·5—102·5°.

A 1 : 1 mixture of (+)-sulphone-A and (−)-sulphone-A was optically inactive, and had m. p. 117—118° alone and when mixed with (±)-sulphone-A.

trans-1 : 2-*Dibenzoylethylene*. This compound (from National Aniline Division, Allied Chemical and Dye Corporation, New York) (7·6 g.), toluene-ω-thiol (4·0 g.), and ascaridole (2 drops) were heated under coal-gas for 5½ hr. The whole was allowed to crystallise from ethanol, and yielded *benzyl* 1 : 2-*dibenzoylethyl sulphide* (9·9 g.), needles, m. p. 97·5—98·5°, which after two further crystallisations had m. p. 99° (Found: C, 76·5; H, 5·55; S, 8·7. $C_{23}H_{20}O_2S$ requires C, 76·6; H, 5·6; S, 8·9%).

trans-1 : 2-Dibenzoylethylene (3·63 g.) and (±)-1-phenylpropane-2-thiol (2·43 g.) were heated with ascaridole (2 drops) under nitrogen for 6½ hr. From a solution of the resultant oil in ethanol there separated a product (2·3 g.) having m. p. 80—81°, which after recrystallisation from light petroleum (b. p. 40—60°) and from ethanol yielded (±)-1 : 2-*dibenzoylethyl* α-*methylphenethyl sulphide* (1·27 g.), rhombs, m. p. 87·5° (Found: C, 76·8; H, 6·35; S, 7·95. $C_{25}H_{24}O_2S$ requires C, 77·3; H, 6·2; S, 8·25%). Evaporation of the filtrates gave a crop (0·37 g.), m. p. 84—85°, and an oil (3·2 g.). Similar reaction of the ethylene (3·33 g.) and the (±)-thiol (2·15 g.) gave solid sulphide (2·17 g.), m. p. 80—81°, and oil (2·8 g.).

(±)-1 : 2-Dibenzoylethyl α-methylphenethyl sulphide (oil; 0·40 g.), in acetic acid (5 ml.), was heated for 5 min. with hydrazine hydrate (100%; 4 drops). The solution was diluted (to 15 ml.) with water and air was aspirated through it for 10 min. The solid product, on crystallisation from chloroform–ethanol (1 : 5), gave a material (0·27 g.), m. p. 130—135°, containing sulphur, recrystallisation of which was accompanied by an odour of thiol and gave a product having m. p. 215—217°; it did not contain sulphur, and on further crystallisation yielded 3 : 6-diphenylpyridazine, m. p. 223—223·5° (Paal and Schulze [7] record m. p. 221—222°).

Oxidation of the sulphides. (±)-1 : 2-Dibenzoylethyl α-methylphenethyl sulphide (oil; 2·7 g.), in acetic acid (20 ml.), was heated for 10 min. with hydrogen peroxide (10 ml.). The solution, on being cooled to 0°, deposited yellow needles (0·4 g.), m. p. 103·5—105·5°, which after two crystallisations from ethanol had m. p. 109—110° and m. p. 111—112° when mixed with *trans*-1 : 2-dibenzoylethylene having m. p. 111·5°. On dilution of the filtrate with water (500 ml.) a further 0·9 g. of dibenzoylethylene was obtained.

The above sulphide (2·2 g.) was kept for 16 hr. at room temperature in acetic acid (20 ml.) containing hydrogen peroxide (4 ml.). An oil having separated, the whole was heated for 2 min., becoming homogeneous; the solution was poured into cold water (1 l.). The solid product was collected and recrystallised from methanol, yielding (±)-1 : 2-*dibenzoylethyl* α-*methylphenethyl sulphone* (1·2 g.), m. p. 116°, which on further crystallisation formed rhombs, m. p. 122·5—123° (Found: O, 15·15; S, 7·55. $C_{25}H_{24}O_4S$ requires O, 15·25; S, 7·6%).

The (±)-sulphide of m. p. 87·5° was oxidised as in the last two experiments. On being heated with hydrogen peroxide this sulphide (0·68 g.) gave *trans*-1 : 2-dibenzoylethylene (0·17 g.), m. p. and mixed m. p. 108—109·5°. In the cold, the sulphide (0·25 g.) yielded (±)-sulphone

[7] Paal and Schulze, *Ber.*, 1900, **33**, 3795.

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(0·12 g.), m. p. 115—116°, which after two recrystallisations from methanol had m. p. 119—120°, mixed m. p. 122°.

A solution of (±)-1 : 2-dibenzoylethyl α-methylphenethyl sulphide (m. p. 87·5°; 0·50 g.) in acetic acid (10 ml.) was heated for 1 hr. and then poured into ice-water (50 ml.). The sulphide (0·41 g.) was recovered, having m. p. and mixed m. p. 86—87°. From the similar treatment of a solution of the (±)-sulphone (0·25 g.), in acetic acid (12 ml.), there was recovered sulphone (0·22 g.), m. p. 117—119°; after recrystallisation from methanol it (0·19 g.) had m. p. and mixed m. p. 121—122°.

Benzyl 1 : 2-dibenzoylethyl sulphide (4·0 g.), in acetic acid (30 ml.), was heated for 10 min. with hydrogen peroxide (20 ml.). From the cooled solution there separated crystals (2·7 g.), fractional crystallisation of which from ethanol gave two crops (total 1·75 g.) of m. p. 173·5—175·5°, and two (total 0·80 g.) of m. p. 97·5—103·5°. Further crystallisation of the former yielded *benzyl* 1 : 2-*dibenzoylethyl sulphone*, needles, m. p. 175·5° (Found: C, 70·5; H, 5·3; S, 8·25. $C_{23}H_{20}O_4S$ requires C, 70·4; H, 5·15; S, 8·15%), and of the latter, *trans*-1 : 2-dibenzoylethylene, m. p. 108·5—111°, mixed m. p. 110—112°.

The preceding sulphide (1·0 g.), acetic acid (20 ml.), and hydrogen peroxide (3·5 ml.) were heated for 2 min. The homogeneous solution obtained was chilled in ice-water, then allowed to attain room temperature overnight. There separated benzyl 1 : 2-dibenzoylethyl sulphone (0·9 g.), m. p. 165°; after recrystallisation from ethanol it (0·77 g.) had m. p. 175·5°.

A solution of benzyl 1 : 2-dibenzoylethyl sulphide (1·0 g.) in acetic acid (10 ml.) was heated for 2 hr., then diluted with water (15 ml.); the sulphide (0·97 g.) was recovered, having m. p. 95·5° and mixed m. p. 98·5°. A solution of benzyl 1 : 2-dibenzoylethyl sulphone (0·34 g.) in acetic acid (10 ml.) was similarly treated; the sulphone (0·30 g.) was recovered, having m. p. 171·5°, mixed m. p. 172·5°.

4′-Nitrochalkone.—This compound (m. p. 149—150°; 2·1 g.) and toluene-ω-thiol (1·0 g.) were heated with ascaridole (2 drops) under coal-gas for 5½ hr. The mixture was allowed to crystallise from light petroleum (b. p. 40—60°), and yielded a product (2·6 g.), m. p. 81—82°, which after three recrystallisations from ethanol gave *benzyl* 2-p-*nitrobenzoyl*-1-*phenylethyl sulphide*, needles, m. p. 87° (Found: N, 3·7; S, 8·5. $C_{22}H_{19}O_3NS$ requires N, 3·8; S, 8·05%).

4′-Nitrochalkone (8·4 g.) and (±)-1-phenylpropane-2-thiol (5·1 g.) were heated under nitrogen with ascaridole (4 drops) for 6 hr. From a solution of the product, an oil, in ethanol, there separated material (10·0 g.), m. p. 48—49°, which, after two crystallisations from methanol and four from *cyclo*hexane yielded (±)-α-*methylphenethyl* 2-p-*nitrobenzoyl*-1-*phenylethyl sulphide* (0·65 g.), needles, m. p. 81—82° (Found: C, 71·1; H, 5·9; S, 7·3. $C_{24}H_{23}O_3NS$ requires C, 71·15; H, 5·7; S, 7·9%).

(−)-2 : 4-*Dinitrophenyl* α-*Methylphenethyl Sulphone.*—(−)-1-Phenylpropane-2-thiol (α^{17}_{5893} −5·88°; *l* 0·5) (1·95 g.), chloro-2 : 4-dinitrobenzene (2·6 g.) and sodium hydroxide (0·5 g.) were heated in ethanol (17·5 ml.) and water (2·5 ml.) for 10 min. The hot solution was filtered, and from the filtrate there separated (−)-2 : 4-*dinitrophenyl* α-*methylphenethyl sulphide* (3·2 g.), yellow rhombs, m. p. 84°, which after two recrystallisations from ethanol had m. p. 88°, $[\alpha]^{21}_{5893}$ −82·5° (*c* 4·848) (Found: N, 8·85; S, 9·85. $C_{15}H_{14}O_4N_2S$ requires N, 8·8; S, 10·05%).

The (±)-thiol (0·87 g.) similarly gave a (±)-*sulphide* (1·68 g.), m. p. 87—89°, which, after two recrystallisations from ethanol, formed yellow rhombs, m. p. 93—94° (Found: N, 8·9; S, 10·15%).

The above (−)-sulphide (1·2 g.), heated for 1½ hr. with hydrogen peroxide (5 ml.) in acetic acid (10 ml.), gave (−)-2 : 4-*dinitrophenyl* α-*methylphenethyl sulphone* (0·5 g.), needles, m. p. 169°, $[\alpha]^{19}_{5893}$ −32·2° (*c* 3·165). Crystallisation from ethanol did not change these constants (Found: O, 27·3; S, 8·85. $C_{15}H_{14}O_6N_2S$ requires O, 27·4; S, 9·15%).

A solution of the (−)-sulphone (0·457 g.) in acetic acid of m. p. 16·45° (7·4 ml. at 20°) was placed in a 1-dm. jacketed polarimeter tube with sealed end-plates, kept at 100° by steam. In 8½ hr. α^{100}_{5893} −0·62° changed only to −0·60°. The solution was poured into cold water (200 ml.); there was recovered (−)-2 : 4-dinitrophenyl α-methylphenethyl sulphone (0·42 g.), $[\alpha]^{17}_{5893}$ −32·8° (*c* 5·010), m. p. and mixed m. p. 165°.

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BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, March 6th,* 1957.]

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678. *Olefin Co-ordination Compounds. Part V.*[1] *Some Diene Complexes of Palladium*(II) *and their Alkoxy-derivatives.*

By J. CHATT, (MISS) L. M. VALLARINO, and L. M. VENANZI.

Compounds of the types [diene PdX_2], [(diene·OR)$_2Pd_2X_2$], and [(diene·OR), *p*-toluidine PdCl] have been prepared. Their properties indicate that they have similar structures to those of their platinous analogues. Generally, the compounds are more deeply coloured, more easily formed, more reactive, and less stable than the corresponding platinous compounds. The alkoxy-derivatives are the first strictly organometallic derivatives of palladium to be reported.

IN Part IV [1] we recorded the preparation of a number of chelated platinous complexes of the type [diene $PtCl_2$] and their conversion into alkoxy-derivatives of the type [(diene·OR)$_2Pt_2Cl_2$]. It was interesting to see whether palladium(II) would give similar derivatives and how they compared with their platinum analogues.

Stable diene derivatives were obtained from the cyclic diolefins *cyclo*octa-1 : 5-diene, C_8H_{12}, and di*cyclo*pentadiene, $C_{10}H_{12}$, but not from dipentene, $C_{10}H_{16}$, which reduced palladous salts to the metal. The compounds prepared are listed in the Table.

Diene complexes of palladium(II) *and their alkoxy-derivatives.*

Compound	Decomp. pt.	Description
*cyclo*Octa-1 : 5-diene :		
$C_8H_{12}PdCl_2$	205—210°	Pale orange needles
$C_8H_{12}PdBr_2$	213	Orange-red needles
$(C_8H_{12}\cdot OMe)_2Pd_2Cl_2$	130—135	Very pale yellow
$(C_8H_{12}\cdot OMe)_2Pd_2Br_2$	125—135	Very pale yellow
Di*cyclo*pentadiene :		
$C_{10}H_{12}PdCl_2$	165—170°	Orange needles or plates
$(C_{10}H_{12}\cdot OMe)_2Pd_2Cl_2$	166—170	Yellow plates
$(C_{10}H_{12}\cdot OEt)_2Pd_2Cl_2$	150—160	Yellow plates
$(C_{10}H_{12}\cdot OPr^n)_2Pd_2Cl_2$	150—156	Yellow plates
$(C_{10}H_{12}\cdot OPr^i)_2Pd_2Cl_2$	150—160	Yellow plates
$C_{10}H_{12}\cdot OMe$, *p*-toluidine, PdCl	145—160	White

The *cyclo*octadiene complex with palladous chloride is exceptionally stable. It is rapidly formed by shaking an aqueous solution of ammonium chloropalladite with the diene; this is in contrast to the mono-olefin complexes of palladium(II) which are formed in anhydrous media,[2] and are decomposed in contact with water.

Preparation and Properties of the Complexes, [diene $PdCl_2$].—These complexes are readily prepared by the reaction of the diene with sodium chloropalladite in acetone :

$$\text{diene} + Na_2PdCl_4 \longrightarrow [\text{diene } PdCl_2] + 2NaCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The *cyclo*octadiene complex can also be prepared in alcoholic solutions, but di*cyclo*pentadiene gives the alkoxy-derivative :

$$2C_{10}H_{12} + 2Na_2PdCl_4 + 2ROH \longrightarrow [(C_{10}H_{12}\cdot OR)_2Pd_2Cl_2] + 4NaCl + 2HCl \quad . \quad . \quad . \quad (2)$$

This parallels our observation in the platinous series that di*cyclo*pentadiene gave alkoxy-derivatives more readily than the other dienes. The dichlorides can also be prepared by Karasch, Seyler, and Mayo's method for mono-olefin complexes: [2]

$$[(PhCN)_2PdCl_2] + \text{diene} \longrightarrow [\text{diene } PdCl_2] + 2PhCN$$

As in the platinous series the bromides and iodides are less stable than the chlorides, and of these only $C_8H_{12}PdBr_2$ was obtained pure.

[1] Part IV, *J.*, 1957, 2496.
[2] Kharasch, Seyler, and Mayo, *J. Amer. Chem. Soc.*, 1938, **60**, 882.

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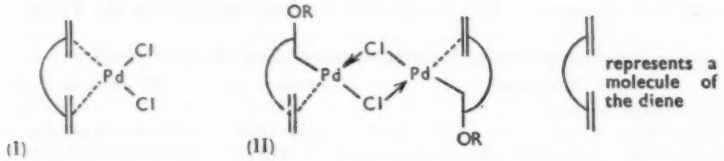
The palladous complexes [diene PdX_2] (X = Cl or Br) are more deeply coloured than their platinous analogues. They are also less stable and more reactive. There is no reason to doubt that they are chelated complexes of type (I), in which the double bonds are perpendicular to the $PdCl_2$ plane, or almost so.

Preparation and Properties of the Alkoxy-derivatives, [(diene OR)$_2$$Pd_2X_2$].—These derivatives are prepared in the same way as their platinous analogues, by the reaction of the dihalide with the appropriate alcohol in presence of anhydrous sodium carbonate :

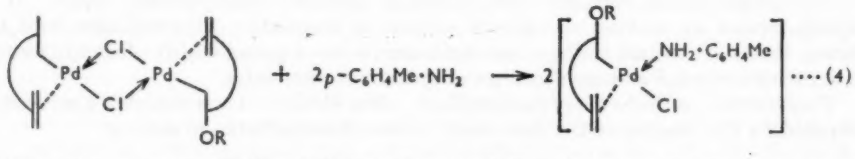
$$2[\text{diene } PdX_2] + 2ROH + 2Na_2CO_3 \longrightarrow [(\text{diene OR})_2Pd_2X_2] + 2NaX + 2NaHCO_3 \quad . \quad . \quad (3)$$

or in the case of di*cyclo*pentadiene complexes also by reaction (2). The alkoxy-chlorides are nicely crystalline and moderately stable. Those of di*cyclo*pentadiene are more thermally stable than those of *cyclo*octadiene. The alkoxy-bromides and -iodides are too unstable to be purified easily although $(C_8H_{12}\cdot OMe)_2Pd_2Br_2$ was obtained pure. The compounds prepared are listed in the Table.

These alkoxy-derivatives are formed more easily than their platinum analogues and, in contrast to their platinum analogues, are readily reconverted into the dichloro-complex, [diene $PdCl_2$], by reaction with hydrochloric acid. [$(C_8H_{12}\cdot OMe)_2Pd_2Cl_2$] and the corresponding bromide are photosensitive.



The palladous complexes are too unstable for so full a structural investigation as was made in the platinous series, but they appear to be exactly analogous. In this case the alkoxy-chlorides will have structures of the type (II) in which PdX·OR has added across one double bond of the diolefin whilst the other remains co-ordinated to the metal atom and approximately perpendicular to the plane of the Pd_2Cl_2 ring. As evidence for the halogen-bridged structure we split the bridge in [$(C_{10}H_{12}\cdot OMe)_2Pd_2Cl_2$] with *p*-toluidine and isolated a simple *p*-toluidine derivative as in the platinous series (reaction 4).



The salts of mercury(II), palladium(II), and platinum(II) are now known to add to olefins in alcoholic solutions to give alkoxy-derivatives, which are true organometallic derivatives of those metals. These show a gradual transition in properties in that order. The mercury compounds are very readily formed, even from mono-olefins, and are very sensitive to hydrochloric acid.[3] Those of platinum are the most difficult to obtain and surprisingly stable to concentrated hydrochloric acid, whereas the palladium compounds show intermediate ease of formation and sensitivity to hydrochloric acid. Thermally the palladium compounds are the least stable.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney of these laboratories.

cyclo*Octa*-1 : 5-*dienedichloropalladium,* [$C_8H_{12}PdCl_2$].—The diene (2 c.c.) was added to a solution of sodium chloropalladite tetrahydrate (2 g.) in methanol (75 c.c.). A yellow precipitate

[3] See Chatt, *Chem. Rev.*, 1951, **48**, 7.

formed almost at once, and after 1 hr. it was filtered off, washed with methanol, and dried. The *complex* recrystallised from glacial acetic acid (yield 1·06 g.) (Found: C, 33·8; H, 4·3. $C_8H_{12}Cl_2Pd$ requires C, 33·6; H, 4·2%). It is sparingly soluble in cold alcohol and benzene, and slightly soluble in hot benzene, chloroform, acetone, ethyl methyl ketone, and diethyl carbonate.

cyclo*Octa*-1 : 5-*dienedibromopalladium*, $[C_8H_{12}PdBr_2]$.—Pure *cyclo*octa-1 : 5-dienedichloropalladium (0·45 g.) and lithium bromide (0·1 g.) in acetone (20 c.c.) were boiled under reflux for 2 hr. The solution was filtered, then taken to dryness at 15 mm., and the solid *complex* washed with water, dried (0·22 g.), and recrystallised from glacial acetic acid (Found: C, 25·8; H, 3·3. $C_8H_{12}Br_2Pd$ requires C, 25·7; H, 3·2%).

Di-(8-*methoxy*cyclo*oct*-4-*enyl*)-μμ′-*dichlorodipalladium*, $[(C_8H_{12}\cdot OMe)_2Pd_2Cl_2]$.—Finely powdered *cyclo*octa-1 : 5-dienedichloropalladium (0·35 g.) was suspended in methanol and heated to the b. p. A small amount of anhydrous sodium carbonate was added and the complex dissolved, giving a very pale yellow solution which was filtered hot. The residue was extracted with a few c.c. of boiling methanol, and the extract added to the bulk of the solution. The *product* separated from this solution on cooling and recrystallised from methanol (this operation must be carried out as rapidly as possible to minimise decomposition) (yield 0·12 g.) (Found: C, 38·6; H, 5·4. $C_{18}H_{30}O_2Cl_2Pd_2$ requires C, 38·4; H, 5·4%).

Di-(8-*methoxy*cyclo*oct*-4-*enyl*)-μμ′-*dibromodipalladium*, $[(C_8H_{12}\cdot OMe)_2Pd_2Br_2]$, was prepared and purified analogously to the methoxychloro-complex from *cyclo*octa-1 : 5-dienedibromopalladium (0·3 g.), anhydrous sodium carbonate, and methanol (yield 0·13 g.) (Found: C, 33·4; H, 4·65. $C_{18}H_{30}O_2Br_2Pd_2$ requires C, 33·2; H, 4·6%).

*Di*cyclo*pentadienedichloropalladium*, $[C_{10}H_{12}PdCl_2]$.—Dibenzonitriledichloropalladium (1 g.), prepared by the method of Kharasch *et al.*,[2] was dissolved in benzene (50 c.c.), and di*cyclo*pentadiene (2 c.c.) added. Orange plates separated during 48 hr. These were filtered off, washed with a small amount of benzene, and dried. The crude *product* was purified by dissolving it in chloroform and reprecipitating it by ether (yield 0·54 g.) (Found: C, 39·2; H, 3·8; Pd, 34·4. $C_{10}H_{12}Cl_2Pd$ requires C, 38·8; H, 3·9; Pd, 34·4%). The same product is also obtained on adding di*cyclo*pentadiene (2 c.c.) to a solution of sodium chloropalladite tetrahydrate (1·3 g.) in acetone (30 c.c.) and keeping the mixture for 24 hr.; the orange solid which formed was filtered off, washed with acetone and water, and dried. It was purified as above (yield 0·72 g.).

Bis(di*cyclopentadienemethoxide*)-μμ′-*dichlorodipalladium*,* $[(C_{10}H_{12}\cdot OMe)_2Pd_2Cl_2]$.—Di*cyclo*pentadiene (3 c.c.) was added to a solution of sodium chloropalladite tetrahydrate (2 g.) in methanol (10 c.c.), and the mixture left overnight. The solid *complex* which had separated was filtered off, washed with methanol, water, dried, and purified by dissolving it in boiling chloroform and diluting the solution with ether (yield 0·92 g.) (Found: C, 43·3; H, 5·0. $C_{22}H_{30}O_2Cl_2Pd_2$ requires C, 43·3; H, 5·0%). It is slightly soluble in cold chloroform and benzene. It is also obtained by shaking di*cyclo*pentadienedichloroplatinum (0·27 g.) with methanol (25 c.c.) for 2 hr. (yield 0·2 g.).

The following complexes were prepared and purified analogously to the methoxy-complex from sodium chloropalladite tetrahydrate, di*cyclo*pentadiene, and the corresponding alcohol:

Bis(dicyclo*pentadiene-ethoxide*)-μμ′-*dichlorodipalladium*, $[(C_{10}H_{12}\cdot OEt)]_2Pd_2Cl_2]$ (0·81 g. from 1 g. of palladite) (Found: C, 44·9; H, 5·4. $C_{24}H_{34}O_2Cl_2Pd_2$ requires C, 45·2; H, 5·4%), slightly more soluble than its methyl analogue.

Bis(di*cyclopentadiene*-n-*propoxide*)-μμ′-*dichlorodipalladium*, $[(C_{10}H_{12}\cdot OPr^n)_2Pd_2Cl_2]$ (0·7 g. from 1 g. of palladite) (Found: C, 46·5; H, 5·8. $C_{26}H_{38}O_2Cl_2Pd_2$ requires C, 46·9; H, 5·75%), appreciably more soluble than its methoxy-analogue.

Bis(di*cyclopentadieneisopropoxide*)-μμ′-*dichlorodipalladium*, $[(C_{10}H_{12}\cdot OPr^i)_2Pd_2Cl_2)$ (0·86 from 1·5 g. of palladite) (Found: C, 46·6; H, 5·8. $C_{26}H_{38}O_2Cl_2Pd_2$ requires C, 46·9; H, 5·75%), less soluble than its *n*-propoxy-analogue.

*Di*cyclo*pentadienemethoxide*-p-*toluidinechloropalladium*, $[C_{10}H_{12}\cdot OMe,p$-toluidine PdCl].—*p*-Toluidine (1 g.) was added to a suspension of the methoxychloro-complex (1 g.) in chloroform (15 c.c.). The resulting solution was cooled to −70° and diluted with light petroleum (b. p. 40—60°) which had been cooled to −70°. Scratching the walls of the vessel and keeping the mixture at −70° afforded a white microcrystalline powder. This *complex* was filtered off,

* Trivial names of this type have been adopted because it is not known which double bond in the diene has been destroyed.

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washed with light petroleum which had been cooled to −70°, and dried (yield 0·44 g.) (Found: C, 52·5; H, 6·1; N, 3·7. $C_{18}H_{24}ONClPd$ requires C, 52·5; H, 5·9; N, 3·4%).

Reaction of Bis(dicyclopentadienemethoxide)-μμ′-dichlorodipalladium with Concentrated Hydrochloric Acid.—The complex (0·44 g.) was shaken in concentrated hydrochloric acid (20 c.c.) for 15 min. The orange solid was filtered off, washed with acetone and ether, and dried. The crude product was purified by dissolving it in hot chloroform and diluting the solution with ether (yield 0·2 g.). Its infrared spectrum was identical with that of dicyclopentadienedichloropalladium.

The authors thank Mr. D. Rosevear for experimental assistance.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, AKERS RESEARCH LABORATORIES, THE FRYTHE, WELWYN, HERTS.
INORGANIC CHEMISTRY LABORATORY, SOUTH PARKS ROAD, OXFORD.
[Present address of Miss L. M. V.: UNIVERSITÀ DI MILANO, ISTITUTO DI CHIMICA GENERALE, VIA SALDINI 50, MILAN, ITALY.] [*Received, March 7th*, 1957.]

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679. *The Chemistry of Santonin. Part IV.* Some Irradiation Products of the Santonins.*

By WESLEY COCKER, K. CROWLEY, J. T. EDWARD, T. B. H. MCMURRY, and E. R. STUART.

The chemistry of the compounds obtained by the irradiation of aqueous solutions of potassium santoninate and potassium 11β(H)-santoninate with ultraviolet light is discussed.

THE action of sunlight on santonin (I) has been the subject of considerable study. Francesconi and Maggi [1] isolated photosantonic acid, $C_{15}H_{22}O_5$, a dibasic acid, from a solution of santonin containing one equivalent of potassium hydroxide, which had been exposed to sunlight. The corresponding lactone, photosantonolactonic acid, $C_{15}H_{20}O_4$, was obtained when photosantonic acid was heated. When, however, a solution of santonin containing three equivalents of potassium hydroxide was exposed to sunlight, photosantoninic acid, $C_{30}H_{42}O_9$, was obtained. Irradiation of an ethanolic solution of santonin gave [2] photosantonin, the ethyl ester of photosantonolactonic acid, as well as photosantonic acid, and a further compound, $C_{17}H_{24}O_4$, whilst irradiation of an acetic acid solution of santonin gave yet another compound, $C_{30}H_{38}O_7$, photosantonic acid, and *iso*photosantonic acid. The lactone of the latter acid has recently been shown [3] to have structure (II), which has been assigned by Perold [4] to geigerin, the bitter principle of the so-called vomiting bush.

We have found that when potassium santoninate in neutral aqueous solution is subjected to the light from a 500 watt ultraviolet lamp, and the product acidified, a monobasic acid, $C_{15}H_{20}O_4,H_2O$ is obtained as the main crystalline product. We propose to name it lumisantoninic acid, and on the basis of evidence described below, assign to it structure (III).

The acid displays ultraviolet absorption maxima at 2480 (log ε 3·7) and 3350 Å (log ε 2·37), indicative of a trisubstituted C=C conjugated with a C=O grouping. The intensity of absorption at the higher wavelength is unusually high although a somewhat similar intensity (log ε 2·59 and 2·32 at 2930 Å) was encountered by Herout and Šorm [5] in the case of the unsaturated, but not conjugated lactones, oxopelenolide-a and -b. Peaks in the infrared spectrum (in Nujol) which occur at 3550 (OH), 2600 (CO_2H), 1728 (CO_2H), 1695 (αβ-unsaturated ketone), and 1576 cm.$^{-1}$ (ethylenic linkage of αβ-unsaturated ketone) are in agreement with structure (III).

Whilst the acid readily affords its lactone, lumisantonin, $C_{15}H_{18}O_3$ (IV), when heated

* Part II, *J. Pharm. Pharmacol.*, 1956, **8**, 1097; Part III, *J.*, 1956, 4549.

[1] Francesconi and Maggi, *Gazetta*, 1903, **33**, II, 65.
[2] Villauechia, *Atti R. Accad. Lincei*, 1885, IV, **1**, 723; *Ber.*, 1885, **18**, 2861.
[3] Barton, de Mayo, and Shafiq, *J.*, 1957, 929.
[4] Perold, *J.*, 1957, 47.
[5] Herout and Šorm, *Chem. Listy*, 1956, **50**, 586; *Coll. Czech. Chem. Comm.*, 1956, **21**, 1494.

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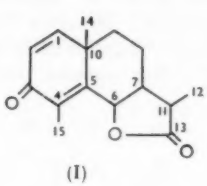
alone or with acetic anhydride, lactonisation also takes place quantitatively with cold ethereal diazomethane. The presence of a γ-hydroxyl group is thus established. Lactonisation of the acid involves loss of two molecules of water, the second of which is present in the acid as hydrate. The lactone has ultraviolet and infrared spectra similar to those of its acid. Thus it shows maxima (in EtOH) at 2400 (log ε 3·67) and 3380 Å (log ε 2·41) and (in $CHCl_3$) at 1772 (butanolide), 1696 (keto), and 1572 cm.$^{-1}$ (C=C).

Ozonolysis of the lactone (IV) gives a gum which rapidly reduces Tollens's reagent, and gives a positive iodoform reaction. Tests for aldehyde were negative.

Reduction of lumisantoninic acid (III) and its lactone (IV) over palladised charcoal or Adams catalyst affords dihydrolumisantoninic acid (V) and dihydrolumisantonin (VI). The keto-group is reduced in small yield by the latter catalyst, but only after very long periods. This fact indicates distortion in the molecule and is reminiscent of the chemistry of santonic acid,[6] a contrast to the case of santonin itself which readily yields hexahydroderivatives with the platinum catalyst.[7] Dihydrolumisantonin (VI) can also be obtained from dihydrolumisantoninic acid (V) by heating it alone or with acetic anhydride or by treating it with ethereal diazomethane.

Dihydrolumisantoninic acid (V) exhibits an ultraviolet maximum at 2825 Å (log ε 1·96) which is characteristic of an isolated keto-group. A second peak at 2220 Å (log ε 3·74) indicates some measure of conjugation. The fact that the acid is inert to ozone, osmium tetroxide, and catalytic reduction eliminates an αβ-unsaturated acid structure. Dihydrolumisantonin (VI), also inert to the reagents mentioned, shows no peak at 2220 Å, but the intensity at this wavelength is high (log ε 3·74). It is not an αβ-butenolide which would show a peak with higher intensity and at a higher wavelength.[8] The infrared spectrum of the acid (V) includes maxima at 3600, 1725, and 1690 cm.$^{-1}$ (CO_2H and CO), but no ethylenic absorption, whilst the lactone (VI) show strong bands at 1778 (butanolide) and 1712 cm.$^{-1}$ (isolated keto-group in a six-membered ring), and no unsaturation.

The analytical data for lumisantonin and its acid require, however, that there should be either a second carbon–carbon double bond or a further ring system, but lumisantonin gives only a dihydroxy-derivative with osmium tetroxide.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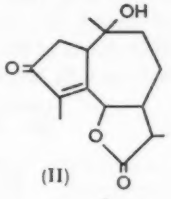
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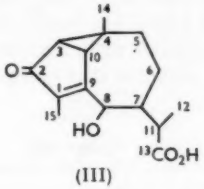
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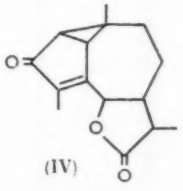
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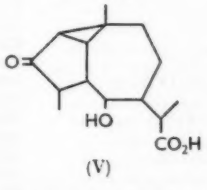
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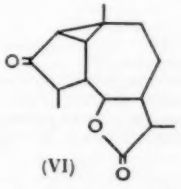
(VI)

The facts detailed above strongly suggest that lumisantonin and its dihydro-derivative, and the corresponding acids, have a *cyclo*propane system conjugated with the keto-group, as portrayed in the formulæ (III), (IV), (V), and (VI). This idea is reinforced by the fact that dihydrolumisantonin and its acid have spectra similar to that of dihydroumbellulone,[9]

[6] Simonsen, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 292.
[7] Cocker and McMurry, *J.*, 1956, 4549.
[8] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[9] Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115; Eastman and Freeman, *ibid.*, 1955, **77**, 6642; Hawthorne, *J. Org. Chem.*, 1956, **21**, 1523.

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a similarity which is absent from the spectra of the isomerisation products (XIV) and (XIX) (see below). Again dihydrolumisantonin semicarbazone ($\lambda_{max.}$ 2380 Å, log ε 4·38) and the semicarbazones of carone ($\lambda_{max.}$ 2355 Å, log ε 4·14) and dihydroumbellulone [9] have similar spectra which are characteristic of a ketone semicarbazone group conjugated with the *cyclo*propane system. The semicarbazone of the isomerisation product (XIX) shows the absorption ($\lambda_{max.}$ 2280 Å, log ε 4·25) of an isolated ketone semicarbazone. Further evidence suggesting the presence of the conjugated *cyclo*propane system comes from the spectrum of the 2 : 4-dinitrophenylhydrazone of dihydrolumi-11β(H)-santoninic acid (Vβ; see below) whose maximum absorption is at 3725 Å (log ε 4·28) (cf. Hawthorne [9]).

As mentioned above, extended reduction of lumisantoninic acid (III) over Adams catalyst affords an acid, $C_{15}H_{24}O_4$, probably the acid of the lactone (VII), in very small yield. It shows no maximum in the ultraviolet region (log ε 2·32 at 2210 Å). By contrast, treatment of dihydrolumisantonin (VI) with potassium borohydride readily gives the olefin (VIII) in good yield, formed presumably from the alcohol (VII). The structure of the olefin is demonstrated by ozonolysis to a product possessing the properties of a methyl ketone (positive iodoform reaction) and aldehyde (positive Schiff's test), and showing infrared maxima (in $CHCl_3$) at 1720 (ketone), 1770 (lactone), and 2750 cm.$^{-1}$ (aldehyde). Such dehydration is unusual but may result from release of strain in the molecule

Reduction of lumisantoninic acid (III) over Raney nickel in an autoclave, followed by dehydrogenation of the product, afforded 7-ethyl-1-methylnaphthalene in high yield. Traces of azulene were also formed but not characterised.

The experiments described above indicate that lumisantoninic acid (III) and lumisantonin (IV) possess either the original eudesmane skeleton of santonin or a closely related ring system, together with the 4-en-3-one system.

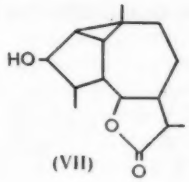
Lumisantonin has three methyl groups. This is shown by a comparison of the intensity of the methyl bands [10] at 1383 cm.$^{-1}$ in a number of santonin derivatives (see Table). Further, the products formed by rearrangement of lumisantonin with hydrogen chloride and with deuterium chloride have identical intensities in the 1456 cm.$^{-1}$ (CH_2) band and in the 1383 cm.$^{-1}$ (CH_3) band, thus showing that no new methyl or " unperturbed " [11] methylene group has been produced during the rearrangement. However, the information to be gained from intensity measurements of the 1456 cm.$^{-1}$ band is of limited value, since it is probable that groups other than CH_2 contribute to this complex peak.[11]

Compound	Infrared max. (cm.$^{-1}$) (Me ~1383)	ε_e	No. of Me	ε_e/Me
Santonin	1382	64	3	21
,,	1385	67·5	3	22·5
,,	1383	66	3	22
,,	1382	69	3	23
Lumisantonin (IV)	1383	63	3	21
Dihydrolumisantonin (VI)	1382	50	3	17
(XIV); HCl rearrangement product of (IV)	1384	81	3	27
DCl rearrangement product of (IV)	1384	81	3	27
(XIX); HCl rearrangement product of (VI)	1383	50	3	17
DCl rearrangement product of (VI)	1383	50	3	17
(XVII)	1382	38	2	19
Limonene	1373	35	2	17·5
Marrubiin [12]	1386	54	3	18

Several rational formulæ may be suggested for lumisantonin. Thus the *cyclo*propane (IX), which could arise from santonin by a light-catalysed Michael-type addition of the $C_{(14)}$-anion to the 1 : 2-double bond might show some transannular conjugation. This, however, has only two methyl groups. Models show that (X), a structure related to

[10] Barton, Page, and Warnhoff, *J.*, 1954, 2715.
[11] Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; Jones, Cole, and Nolin, *ibid.*, p. 5662.
[12] Cocker, Cross, Duff, Edward, and Holley, *J.*, 1953, 2540; Burn and Rigby, *Chem. and Ind.*, 1955, 386.

santonic acid (XI),[13] is sterically impossible. The same objection applies to (XII).[13] Further, the lactone (XIII) formed by reduction of santonic acid with borohydride is unaffected by the acidic conditions under which lumisantonin is rearranged.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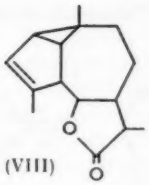
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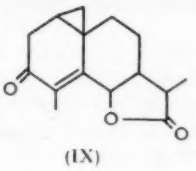
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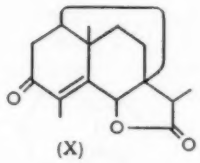
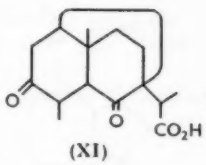

(X)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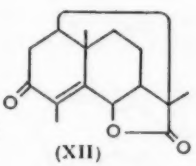
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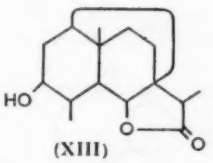
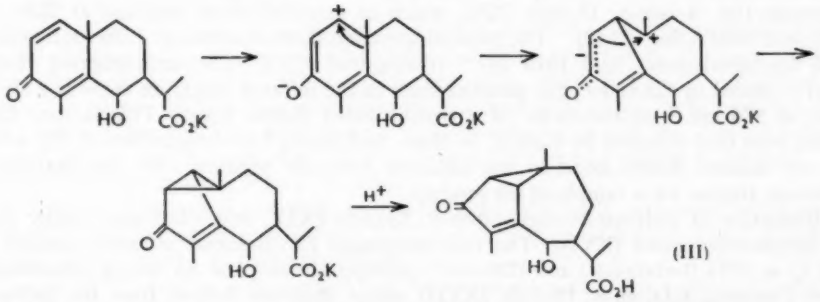

(XIII)

We believe that lumisantonin is best expressed by (IV) and its acid by (III).* These compounds can be produced from santonin by the series of photocatalysed reactions shown in the annexed scheme (cf. ref. 3). In structures (III) and (IV) the ring system is rather strained which is probably responsible for the unusual intensities of the ketone bands in the ultraviolet spectrum. The conjugation of the *cyclo*propane system with the ketone group accounts for the maximum at 2220 Å shown by dihydrolumisantoninic acid (V), though the degree of conjugation is susceptible to small increases in ring strain, since the peak does not appear in the corresponding lactone (VI).

*cyclo*Propanes are well known to undergo cleavage with mineral acids. It is not surprising therefore that lumisantonin (IV) and its dihydro-derivative (VI) undergo isomeric change with acid. Treatment of the former with hydrogen chloride in chloroform [14] gives the guaienolide, 4-chloro-2-oxoguai-9-en-8 : 13-olide (XIV), and a new active carbon–carbon double bond is created. This lactone (XIV) shows infrared maxima


(III)

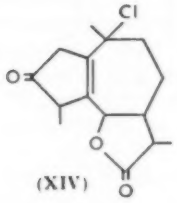
(in $CHCl_3$) at 1778 (butanolide), 1753 (*cyclo*pentanone), and 1620 cm.$^{-1}$ (isolated C=C). In the ultraviolet spectrum there is a maximum at 2970 Å (log ε 1·48). Ozonolysis affords a gum which gives a green ferric reaction, and reduces Tollens's reagent (potential α-ketol), but fails to reduce Schiff's reagent. Conclusive evidence that this acid-catalysed isomeric

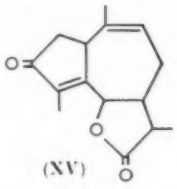
* An alternative formulation with the $C_{(14)}$ transposed from $C_{(4)}$ to $C_{(10)}$ does not account so well for the formation of the acid-catalysed isomerisation products.

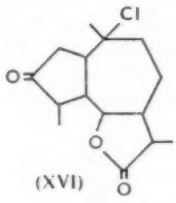
[13] Woodward, Brutschy, and Baer, *J. Amer. Chem. Soc.*, 1948, **70**, 4216.
[14] Barton, *J.*, 1951, 1444; cf. Büchi and White, *J. Amer. Chem. Soc.*, 1957, **79**, 750.

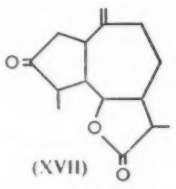
XUM

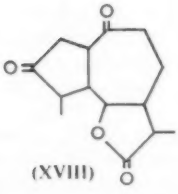
change takes place, and that the product is a guaienolide comes from the fact that when boron trifluoride in acetic acid is the isomerising agent lumisantonin affords 4-acetoxy-2-oxoguai-1(9)-en-8 : 13-olide, the acetate of (II). This compound is obtained along with *iso*photosantonic acid lactone (II) [2,3] when santonin is irradiated in aqueous acetic acid (cf. Barton, de Mayo, and Shafiq [3]). The acetate shows absorption at 2370 (log ε 4·2) and

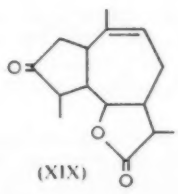

(XIV)

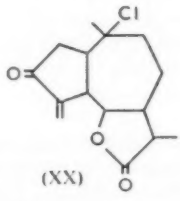

(XV)

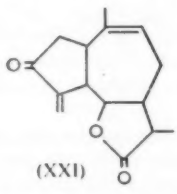

(XVI)


(XVII)


(XVIII)


(XIX)


(XX)


(XXI)

3090 Å (log ε 1·73). The unsaturated compound 2-oxoguai-1(15) : 4-dien-8 : 13-olide (XXI) is also obtained in the isomerisation. The latter shows maximum absorption at 2195 (log ε 4·14) and 3245 Å (log ε 1·91) in the ultraviolet and at 1775 (lactone), 1716 (*cyclo*pentenone), 1647 and 1602 (C=C), 925($>$C=CH$_2$), and 832 cm.$^{-1}$ ($-\overset{|}{C}$=CH) in the infrared spectrum.

Further evidence for the azulenic nature of the isomerisation products mentioned above arises from the fact that when the unsaturated lactone (XIX) is reduced with lithium aluminium hydride and then dehydrogenated a blue oil, whose spectrum is similar to that of guiazulene or chamazulene, is obtained.

Dehydrochlorination of compound (XIV) gives the conjugated unsaturated ketone, 2-oxoguai-1(9) : 4-dien-8 : 13-olide (XV), which as expected shows maxima at 2375 (log ε 3·8) and 3420 Å (log ε 2·42). The infrared spectrum shows maxima at 1780 (butanolide), 1695 (*cyclo*pentenone), and 1579 cm.$^{-1}$ (conjugated C=C). The unconjugated double bond is placed in the endocyclic position since in the infrared spectrum there is a strong peak at 835 cm.$^{-1}$ characteristic of a trisubstituted double bond. This lactone (XV) differs from that obtained by Barton, de Mayo, and Shafiq [3] by dehydration of (II), which has its isolated double bond in the adjacent exocyclic position. We are grateful to Professor Barton for a sample of his product.

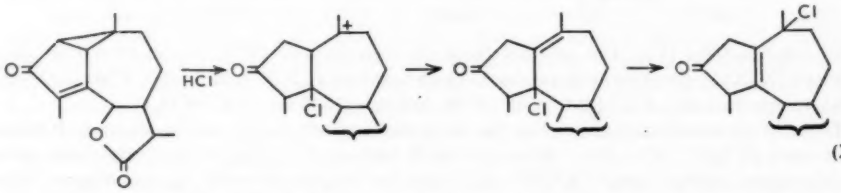
Reduction of 4-chloro-2-oxoguai-9-en-8 : 13-olide (XIV) over platinum rapidly gives its dihydro-compound (XVI). The new compound (XVI) shows infrared maxima (in $CHCl_3$) at 1774 (butanolide) and 1739 cm.$^{-1}$ (*cyclo*pentanone), and on dehydrochlorination gives 2-oxoguai-4(14)-en-8 : 13-olide (XVII) whose structure follows from the following evidence. It shows a single ultraviolet maximum at 2950 Å (log ε 1·69), and infrared maxima at 1775 (butanolide), 1742 (*cyclo*pentanone), and 1630 cm.$^{-1}$ (isolated C=C). The intensity of the methyl peak at 1382 cm.$^{-1}$ (see Table) shows the presence of *two* methyl groups. The exocyclic methylene group is also shown to be present by an infrared band at 908 cm.$^{-1}$. Ozonolysis of this methylene-ketone (XVII) gives the diketo-lactone (XVIII) whose infrared spectrum includes maxima at 1782 (butanolide), 1748 (*cyclo*pentanone), and 1710 cm.$^{-1}$ (*cyclo*heptanone).

Isomerisation of dihydrolumisantonin (VI) with hydrogen chloride in chloroform gives

the unsaturated lactone (XIX), which is not identical with (XVII). The new lactone (XIX) shows a single ultraviolet maximum at 2830 Å (log ε 1·67), and infrared maxima at 1778, 1747, and 1640 cm.$^{-1}$; on ozonolysis it gives an aldehyde (positive Schiff's and Tollens's tests) and a methyl ketone (iodoform). The infrared spectrum of the gum confirms the assignment of structure; it has peaks at 2750 (aldehyde), 1780 (butanolide), 1748 cm.$^{-1}$ (*cyclo*pentanone), 1705 (carbonyl), and 1357 (COMe).

The isomerisation involved in the changes (IV) ⟶ (XIV) and (VI) ⟶ (XIX) by hydrogen chloride produces a new " perturbed " methylene group at $C_{(3)}$. This is shown by the following evidence. Peaks at 1402 (ε_0 40·7) and 1409 cm.$^{-1}$ (ε_0 32·3) in the products (XIV) and (XIX) have appreciably higher intensity than the corresponding peaks (ε_0 17·2 and 18·9 respectively) in the deuterated derivatives, these peaks being due to a methylene group next to a keto-group in a five-membered ring.[11] This evidence may be vitiated by hydrogen exchange, but it is a significant fact that all the isomerised products have a strong band in the 1402—1410 cm.$^{-1}$ region which is either absent or is very weak in the unisomerised compounds.

We envisage the isomerisation of lumisantonin as taking place by the annexed route.



(XIV)

Irradiation of 11β(H)-santoninic acid in presence of one equivalent of alkali gives a compound (A), stereoisomeric with lumisantoninic acid (III). We name it lumi-11β(H)-santoninic acid (IIIβ *). On occasion a second compound (B), $C_{15}H_{20}O_4,H_2O$, was also obtained (see below).

The spectra of lumi-11β(H)-santoninic acid (IIIβ) are similar to those of its isomer (III) (see p. 3426). The existence of the αβ-unsaturated ketone system is confirmed, however, by the formation of a 2 : 4-dinitrophenylhydrazone whose long-wavelength maximum is at 3830 Å (log ε 4·54). Ozonolysis gives a gum which rapidly reduces Tollens's reagent and gives a positive iodoform reaction.

Lumi-11β(H)-santoninic acid affords lumi-11β(H)-santonin (IVβ) on treatment with ethereal diazomethane, and on reduction over palladised charcoal or platinum the acid (IIIβ) affords dihydrolumi-11β(H)-santoninic acid (Vβ), which like its isomer (V) is unaffected by ozone. Dihydrolumi-11β(H)-santoninic acid (Vβ) yields its lactone, dihydrolumi-11β(H)-santonin (VIβ), on treatment with diazomethane, and this lactone may be obtained by the reduction of lumi-11β(H)-santonin (IVβ) over palladised charcoal. Dihydrolumi-11β(H)-santonin is inert to ozone.

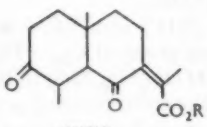
Treatment of dihydrolumi-11β(H)-santoninic acid (Vβ) with potassium borohydride, followed by acidification, affords lactone (VIIβ) and dehydrogenation of this with palladised charcoal gives 7-ethyl-1-methylnaphthalene.

Lumi-11β(H)-santonin is isomerised with hydrogen chloride to the α-methylene-ketone (XX) whose spectrum shows bands at 2215 and 3320 Å (log ε 3·93 and 1·8 respectively) and at 1707 (*cyclo*pentenone), 1775 (lactone), and 1600 cm.$^{-1}$ (C=C). The formation of an αβ-unsaturated ketone (cf. XIV) may be the result of extended treatment with hydrogen chloride. The isomerisation product (XX) is smoothly reduced over platinum to the dihydro-compound (XVIβ), showing maxima at 2980 (log ε 1·54; but log ε 2·0 at 2150 Å) and 1740 cm.$^{-1}$, characteristic of a *cyclo*pentanone. Dehydrochlorination gives a diunsaturated compound, probably (XXIβ), which shows maxima at 2200 (log ε 4·05) and

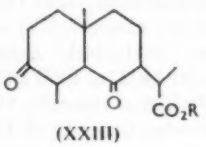
* We use the suffix β to indicate that the compound is obtained from 11β(H)-santonin.

3250 Å (log ε 1·82), characteristic of an αβ-unsaturated ketone, and at 1785 (lactone), 1720 (*cyclo*pentenone), 1645 (C=C), and 1602 cm.$^{-1}$ (C=C).

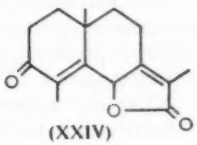
Rearrangement of dihydrolumi-11β(H)-santonin (VIβ) affords an unsaturated compound with a single ultraviolet maximum at 2840 Å (log ε 1·67) and infrared peaks at 1785, 1750 (*cyclo*pentanone), and 1645 cm.$^{-1}$ (C=C). By analogy with the product of isomerisation



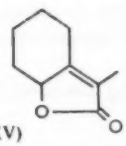
(XXII)



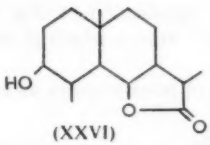
(XXIII)



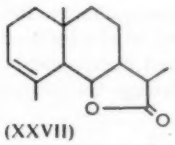
(XXIV)



(XXV)



(XXVI)



(XXVII)

of the lumi-lactone (VI), the product from its stereoisomer (VIβ) is considered to have structure (XIXβ); its ozonolysis product shows maxima at 2750 (aldehyde), 1780 (lactone), 1748 (*cyclo*pentanone), 1727 (aldehyde), 1704 (ketone), 1356 cm.$^{-1}$ (CO·CH_3).

The acid (B) mentioned above has the properties expected of 3 : 6-dioxoeudesm-7(11)en-13-oic acid (XXII; R = H). Although itself hydrated ($C_{15}H_{20}O_4$,H_2O) the acid gives an anhydrous methyl ester (XXII; R = Me) on treatment with diazomethane. The acid exhibits maximum ultraviolet absorption at 2180 Å (log ε 4·0), typical of an αβ-unsaturated acid,[15] and at 2900 Å (log ε 1·64) suggestive of an isolated keto-group, whilst a shoulder at 3200 Å (log ε 1·45) suggests an αβ-unsaturated ketone, the low-wavelength absorption of which is probably merged in the band at 2180 Å. In agreement with these interpretations, the acid exhibits maxima (in CH_2Cl_2) at 1712 (C:O and αβ-unsaturated acid), 1690 (αβ-unsaturated ketone) and 1645 cm.$^{-1}$ (C=C). Similar spectral data are manifested by the methyl ester (XXII; R = Me).

The acid (XXII; R = H) does not decolorise bromine in chloroform, but reacts with permanganate in acetone, and is reduced over platinum to give 3 : 6-dioxoeudesman-13-oic acid (XXIII; R = H) in a hydrated form. Reaction of this acid with diazomethane affords its anhydrous methyl ester (XXIII; R = Me) which may also be obtained by the reduction of methyl 3 : 6-dioxoeudesm-7(11)en-13-oate (XXII; R = Me). The reduced acid (XXIII; R = H) shows a single maximum at 2860 Å (log ε 1·6), whilst its ester shows two maxima at 2750 Å (log ε 1·75) and 2950 Å (log ε 1·58) indicative of isolated keto-groups. The reduced acid shows very strong infrared absorption (in $CHCl_3$) at 1715 (C:O and CO_2H) and weaker absorption at 1745 cm.$^{-1}$ (hindered or hydrogen-bonded C:O); the ester shows a single composite maximum at 1720 cm.$^{-1}$ (C:O and CO_2Me). The ester forms a monoxime which exhibits absorption at 1715 (C:O) and 1728 cm.$^{-1}$ (CO_2Me), but no recognisable C=N absorption; this is probably merged in the strong band at 1715 cm.$^{-1}$.

3 : 6-Dioxoeudesm-7(11)-en-13-oic acid (XXII; R = H) is lactonised only with difficulty and in small yield. The lactone (XXIV) shows maxima at 2200 (log ε 4·36) and 3250 Å (log ε 1·6), indicating respectively αβ-butenolide and αβ-unsaturated ketone systems, the low-wavelength absorption of the latter appearing as a shoulder at 2350 Å (log ε 4·37). Dauben and Hance [8] found that the αβ-butenolide (XXV) exhibits maximum absorption at 2170 Å (log ε 4·24). The infrared absorption of the lactone (XXIV) supports its structure, having maxima at 1758 (αβ-butenolide), 1700 (C:O), 1686 cm.$^{-1}$ (C=C). Dauben and

[15] Barton and Seoane, *J.*, 1956, 4150; Cram and Allinger, *J. Amer. Chem. Soc.*, 1956, **78**, 5275.

Hance,[8] and Cocker, Cross, and Hayes,[16] respectively, found that the analogue (XXV) exhibited maxima at 1757 and 1750 cm.$^{-1}$.

3 : 6-Dioxoeudesman-13-oic acid (XXIII; R = H) is reduced by potassium borohydride, *four* hydrogen atoms being taken up, to give 3-hydroxyeudesman-6 : 13-olide (XXVI), which shows no significant ultraviolet absorption, but maxima at 3570 (OH) and 1754 cm.$^{-1}$ (lactone). Dehydrogenation of the lactone affords 7-ethyl-1-methylnaphthalene characterised as its picrate.

Dehydration of 3-hydroxyeudesman-6 : 13-olide (XXVI) with phosphorus oxychloride and pyridine gives the olefin (XXVII) which shows end-absorption at 2200 Å (log ε 2·01), and a maximum at 1760 cm.$^{-1}$ (butanolide). Ozonolysis of the olefin gives a gum which gives a positive Schiff's test, gives iodoform, and has infrared peaks at 2750 (aldehyde), 1770 (lactone), and 1720 cm.$^{-1}$ (C:O).

Experimental

Ultraviolet spectra were measured in ethanol solutions with a Beckman D.U. instrument, and the infrared spectra with a Hilger 800 double-beam instrument. The irradiations were performed with a Hanovia, 500 w ultraviolet lamp (U.V.S. 500 model).

Irradiation of Potassium Santoninate.—A mixture of santonin (125 g.), potassium hydroxide (28 g.), and water (500 c.c.) was heated for 45 min. and allowed to cool. The unchanged santonin was collected, and the filtrate was diluted with water to 750 c.c. (pH 8·0) and irradiated in quartz flasks for 48 hr. After 24 hr. the flasks were turned to allow light to enter, a deposit having formed on the sides of the flasks facing the lamp. The solution was extracted with chloroform to remove santonin (14 g.), acidified, and extracted with chloroform (4 × 75 c.c.). The chloroform solution gradually deposited *lumisantoninic acid* (III) (28 g.) as rhombs (from ethyl acetate), m. p. 142—143° (rapid heating), $[\alpha]_D^{21}$ −78·0° (*c* 2·2 in EtOH) (Found : C, 64·4; H, 7·9%; equiv., 278. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·8%; equiv., 282). Concentration of the mother-liquor and addition of ether (150 c.c.) to the residue gave an acid (6 g.) as needles, m. p. 154—155°, probably identical with photosantonlactonic acid (Found : C, 67·5; H, 7·8. Calc. for $C_{15}H_{20}O_4$: C, 68·2; H, 7·6%). Further quantities of lumisantoninic acid (11 g.) were obtained by removal of the ether and addition of ethyl acetate (75 c.c.) to the residue. The residual gum was then heated with acetic anhydride (50 c.c.) for 2 hr., the acetic anhydride removed, and the product dissolved in chloroform. Extraction of the chloroform solution with a saturated solution of sodium hydrogen carbonate gave on acidification more photosantonlactonic acid (14 g.).

Lumisantonin (IV).—(*a*) Lumisantoninic acid (1 g.) in methanol (10 c.c.) was treated with excess of diazomethane in ether. Removal of the solvents gave the *lactone* (IV) (0·5 g.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as plates, m. p. 155—156°, $[\alpha]_D$ −180° (*c* 1·5 in $CHCl_3$) (Found : C, 72·7; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

(*b*) Lumisantoninic acid (0·2 g.) was heated with acetic anhydride (5 c.c.) on a water-bath for 15 min. Removal of the acetic anhydride and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave the lactone (IV) (0·14 g.), m. p. 154—155°.

(*c*) Lumisantoninic acid (1 g.) was heated at 150° for 10 min., to give the lactone (0·75 g.), m. p. 155—156°.

Dihydrolumisantoninic Acid (V).—(*a*) A mixture of lumisantoninic acid (1 g.), platinum oxide (0·2 g.), and ethyl acetate (100 c.c.) was stirred in hydrogen for 18 hr. The *product* (V) (0·5 g.) crystallised from ethyl acetate as needles, m. p. 146—147°, $[\alpha]_D^{17}$ −30·5° (*c* 1·5 in EtOH) (Found : C, 67·5; H, 7·9. $C_{15}H_{22}O_4$ requires C, 67·6; H, 8·3%).

(*b*) Lumisantoninic acid (1·3 g.) was reduced over platinum oxide (0·2 g.) in ethyl acetate (100 c.c.) for 48 hr., and the products were separated by crystallisation from ethanol, giving dihydrolumisantoninic acid (0·7 g.), m. p. 145—146°, and the *acid* (80 mg.), m. p. 174—175°, log ε 2·32 at 2210 Å (no max.) (Found : C, 66·9; H, 8·6. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%), corresponding to the lactone (VII).

Dihydrolumisantonin.—Lumisantonin (IV) (0·8 g.), platinum oxide (0·1 g.), and ethyl acetate (50 c.c.) were stirred in hydrogen for 18 hr. Crystallisation of the product from ethyl acetate gave *dihydrolumisantonin* (VI) (0·65 g.), as needles, m. p. 161—162°, $[\alpha]_D$ −52·6° (*c*

[16] Cocker, Cross, and Hayes, *Chem. and Ind.*, 1952, 314.

XUM

1·6 in $CHCl_3$) (Found : C, 72·3; H, 7·8. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%) [*semicarbazone*, m. p. 265° (Found : C, 62·8; H, 7·4. $C_{16}H_{23}O_3N_3$ requires C, 62·9; H, 7·5%)].

Reduction of Dihydrolumisantonin.—A solution of dihydrolumisantonin (VI) (1 g.) and potassium borohydride (0·3 g.) in methanol (30 c.c.) and water (5 c.c.) was set aside for 24 hr., then acidified. The product, crystallised from ethanol, gave the *olefinic lactone* (VIII) (0·3 g.) as plates, m. p. 144—145°, $[\alpha]_D^{23}$ −81·9°; (*c* 1·3 in $CHCl_3$) (Found : C, 77·1; H, 8·6. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·7%).

This compound (0·12 g.) in methyl acetate (20 c.c.) was treated with excess of ozone at −20°, and the ozonide was reduced with hydrogen over 10% palladised charcoal (0·1 g.). The product was a gum, which gave positive reactions with Tollens's and Schiff's reagents, and also iodoform with sodium hypoiodite.

Dehydrogenation Experiments.—Lumisantoninic acid (7 g.) in methanol (100 c.c.) was reduced over Raney nickel (1 g.) at 100—120°/80 atm. of hydrogen. The oily product was heated with selenium (10 g.) at 280—300° for 30 hr. The mixture was extracted with ether, and the extract was distilled in steam, to give an oil (1·8 g.), b. p. 140°/20 mm. Redistillation gave an oil whose infrared spectrum was essentially identical with that of 1-ethyl-7-methylnaphthalene. The oil was further characterised by formation of a picrate, m. p. 96—97°, and styphnate, m. p. 126°, both undepressed on admixture with the respective derivatives of 1-ethyl-7-methylnaphthalene.

Oxidation of Lumisantonin with Osmium Tetroxide.—A solution of lumisantonin (IV) (0·11 g.) and osmium tetroxide (0·22 g.) in dioxan (9 c.c.) was set aside for 48 hr. The osmic ester was decomposed by hydrogen sulphide, and the product crystallised from ethyl acetate, to give *dihydrolumisantonindiol* (60 mg.) as rhombs, m. p. 185° (decomp.) (Found : C, 63·6; H, 7·1. $C_{15}H_{20}O_5$ requires C, 64·2; H, 7·2%).

4-*Chloro*-2-*oxoguai*-9-*en*-8 : 13-*olide* (XIV).—Lumisantonin (IV) (1 g.) in chloroform (20 c.c.) was treated with a stream of hydrogen chloride for 4 hr. The solution was washed with sodium hydrogen carbonate, then dried, and the chloroform was removed. Recrystallisation of the product from ethyl acetate–light petroleum (b. p. 60—80°) gave 4-*chloro*-2-*oxoguai*-9-*en*-8 : 13-*olide* (XIV) (0·52 g.) as needles, m. p. 151—152°, $[\alpha]_D^{20}$ −186° (*c* 1·18 in $CHCl_3$) (Found : C, 63·6; H, 6·4. $C_{15}H_{19}O_3Cl$ requires C, 63·7; H, 6·7%).

2-*Oxoguai*-1(9) : 4-*dien*-8 : 13-*olide* (XV).—The previous compound (XIV) (0·2 g.), anhydrous sodium acetate (0·25 g.), and ethanol (15 c.c.) were refluxed for 1 hr. The product was recrystallised from aqueous ethanol, to give 2-*oxoguai*-1(9) : 4-*dien*-8 : 13-*olide* (XV) (60 mg.) as plates, m. p. 150—151°, $[\alpha]_D^{20}$ −136·5° (*c* 0·26 in $CHCl_3$) (Found : C, 72·9; H, 7·1. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

4-*Chloro*-2-*oxoguaian*-8 : 13-*olide* (XVI).—4-Chloro-2-oxoguai-9-en-8 : 13-olide (XIV) (0·8 g.), platinum oxide (0·1 g.), and ethyl acetate (30 c.c.) were stirred in hydrogen for 4 hr. The product, recrystallised from ethanol, was 4-*chloro*-2-*oxoguaian*-8 : 13-*olide* (XVI) (0·6 g.), needles, m. p. 198—199°, $[\alpha]_D^{20}$ −155·7° (*c* 0·53 in $CHCl_3$) (Found : C, 63·0; H, 7·4. $C_{15}H_{21}O_3Cl$ requires C, 63·3; H, 7·4%).

2-*Oxoguai*-4(14)-*en*-8 : 13-*olide* (XVII).—The above compound (XVI) (0·24 g.), anhydrous sodium acetate (0·3 g.), and ethanol (30 c.c.) were refluxed for 4 hr. The product was recrystallised from aqueous ethanol, to give 2-*oxoguai*-4(14)-*en*-8 : 13-*olide* (XVII) (0·1 g.) as rods, m. p. 105—106°, $[\alpha]_D^{23}$ −0·5° (*c* 0·43 in $CHCl_3$) (Found : C, 72·5; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

14-*Demethyl*-2 : 4-*dioxoguaian*-8 : 13-*olide* (XVIII).—2-Oxoguai-4(14)-en-8 : 13-olide (100 mg.) in methyl acetate (15 c.c.) was treated with excess of ozone at −20°. The ozonide was reduced with hydrogen over palladised charcoal, to give 14-*demethyl*-2 : 4-*dioxoguaian*-8 : 13-*olide* (70 mg.) as rhombs, m. p. 180—181° (Found : C, 67·1; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

Ozonolysis of 4-*Chloro*-2-*oxoguai*-9-*en*-8 : 13-*olide* (XIV).—The chloro-ketone (0·1 g.) in methyl acetate (15 c.c.) was treated with excess of ozone at −20°. The ozonide, reduced with hydrogen over palladised charcoal, gave a gum, which gave a negative Schiff's test but positive reactions with ferric chloride and Tollens's reagent and iodoform with sodium hypoiodite.

2-*Oxoguai*-4-*en*-8 : 13-*olide* (XIX).—Dihydrolumisantonin (VI) (0·5 g.) in chloroform (15 c.c.) was saturated with hydrogen chloride for 4 hr. After addition of sodium hydrogen carbonate and filtration, the chloroform was removed, and the product recrystallised from ethanol, to give 2-*oxoguai*-4-*en*-8 : 13-*olide* (XIX) (0·2 g.), plates, m. p. 210—211°, $[\alpha]_D^{20}$ +47·9° (*c* 1·03 in $CHCl_3$)

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(Found: C, 72·2; H, 7·8. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%). The *semicarbazone* had m. p. 246° (Found: C, 62·2; H, 7·6. $C_{16}H_{23}O_3N_3$ requires C, 62·9; H, 7·5%).

Ozonolysis of 2-Oxoguai-4-en-8 : 13-olide (XIX).—Excess of ozone was passed into a solution of this lactone (0·1 g.) in methyl acetate (15 c.c.), and the ozonide reduced with hydrogen over palladised charcoal. The product was a gum, which gave positive reactions with Schiff's and Tollens's reagents, and also iodoform with sodium hypoiodite.

Dehydrogenation Experiment.—2- Oxoguai-4-en-8 : 13-olide (XIX) (0·4 g.), lithium aluminium hydride (1 g.), and dry ether (200 c.c.) were refluxed for 5 hr. The product, a glass (0·4 g.), was isolated in the usual way and heated (0·2 g.) with 10% palladised charcoal (0·13 g.) under nitrogen at 300° rising to 360° during 6 min., and kept at 360° for 6 min. The product was extracted with light petroleum, and the extract washed with 90% phosphoric acid (5 × 3 c.c.). The acid was diluted with water to 150 c.c. and extracted with light petroleum from which a dark blue oil (3·9 mg.), $\lambda_{max.}$ 3730, 3560, 3420, 2910, 2480, and 2320 Å (log ε 2·94, 3·16, 3·2, 4·0, 3·94, and 3·96), was obtained.[17]

Rearrangements with Deuterium Chloride.—(*a*) Deuterium chloride, prepared by dropping deuterium oxide into a mixture of phosphorus pentachloride and sand, was passed into a solution of lumisantonin (0·5 g.) in chloroform, and the whole was kept for 14 hr. The product was deuterated 4-chloro-2-oxoguai-9-en-8 : 13-olide (XIV), m. p. 151—152°, infrared max. at 1778 (butanolide), 1756 cm.$^{-1}$ (*cyclo*pentanone). (*b*) Similar treatment of dihydrolumisantonin gave deuterated 2-oxoguai-4-en-8 : 13-olide (XIX), m. p. 202—207°, infrared max. at 1775 and 1745 cm.$^{-1}$.

Isomerisation of Lumisantonin with Boron Trifluoride.—A mixture of lumisantonin (0·85 g.), acetic acid (10 c.c.), and boron trifluoride–ether complex (2 c.c.) was set aside for 20 hr. The mixture was poured into water and neutralised with sodium hydrogen carbonate. The resulting solid crystallised from ethanol, giving 4-acetoxy-2-oxoguai-1(9)-en-8 : 13-olide as needles (0·2 g.), m. p. and mixed m. p. 181—182°, $[\alpha]_D^{18}$ +56·1° (*c* 1·07 in $CHCl_3$)[2,3] (Found: C, 67·1; H, 6·9. Calc. for $C_{17}H_{22}O_5$: C, 66·7; H, 7·2%) and *2-oxoguai-1(15) : 4-dien-8 : 13-olide*, needles, m. p. 129—130°, $[\alpha]_D^{19}$ −171° (*c* 0·4 in $CHCl_3$) (Found: C, 73·4; H, 7·6. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

Reduction of Santonic Acid.—A solution of santonic acid (0·5 g.) in 0·1N-sodium hydroxide (30 c.c.) was treated with potassium borohydride (0·5 g.) and set aside for 36 hr. Careful acidification gave a gum which was extracted with chloroform, and the extract was washed with dilute aqueous ammonia. Removal of solvent gave the *lactone* (XIII) (0·3 g.), m. p. 153—157°, which after crystallisation from ethyl acetate–light petroleum was obtained as needles, m. p. 158°, $[\alpha]_D^{19}$ +40° (*c* 1·4 in $CHCl_3$) (Found: C, 71·8; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). It showed no ultraviolet absorption maximum.

Photosantoninic Acid.—(*a*) Santonin (8·2 g.) was dissolved in a solution of potassium hydroxide (5·6 g.) in water (100 c.c.) and irradiated for 48 hr. The product obtained on acidification was recrystallised from ethanol three times, to give photosantoninic acid, m. p. 272—273°, $[\alpha]_D^{14}$ −33·0° (*c* 3·3 in $CHCl_3$) (Found: C, 65·8; H, 7·6%; equiv., 270. Calc. for $C_{30}H_{42}O_9$: C, 65·9; H, 7·7%; equiv., 273). (*b*) Lumisantoninic acid (III) (0·2 g.), potassium hydroxide (0·75 g.), methanol (20 c.c.), and water (10 c.c.) were set aside for 24 hr. Acidification of the solution gave photosantoninic acid, m. p. and mixed m. p. 272°.

Action of Acetic Anhydride on Photosantoninic Acid.—The acid (0·3 g.) was heated on the water-bath for 2 hr. with acetic anhydride (15 c.c.), and the excess of anhydride then removed in a vacuum. The product was recrystallised from ethyl acetate, giving the mixed anhydride as needles (0·15 g.), m. p. 199° (Francesconi and Maggi [1] record m. p. 199°) (Found: C, 69·5; H, 7·2; Ac, 7·9. Calc. for $C_{32}H_{40}O_8$: C, 69·5; H, 7·3; 1Ac, 7·8%).

Dihydrophotosantoninic Acid.—Photosantoninic acid (0·5 g.) and platinum oxide (0·1 g.) in ethyl acetate (30 c.c.) were stirred in hydrogen for 48 hr. The product was recrystallised from ethanol, to give *dihydrophotosantoninic acid*, m. p. 275—280°, $[\alpha]_D^{15}$ −42° (*c* 0·6 in $CHCl_3$) (Found: C, 68·1; H, 7·9. $C_{30}H_{42}O_8$ requires C, 67·9; H, 8·0%).

Irradiation of 11β(H)-Santonin.—Dilute aqueous solutions of potassium 11β(H)-santoninate at pH 8 were irradiated and processed as described for potassium santoninate. The chloroform extract of the irradiation products deposited overnight a white powder, m. p. 90—120°. Crystallisation of this from ethyl acetate–light petroleum (b. p. 40—60°) gave two types of

[17] Cf. Čekan, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 798; Treibs and Barchet, *Annalen*, 1950, **566**, 89.

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crystals and by hand-picking large hexagonal plates of (B) **3 : 6-*dioxoeudesm*-7(11)-*en*-13-*oic acid*** (XXII; R = H) were obtained almost pure. Further crystallisation from ethanol gave pure acid (B), m. p. 174—175°, $[\alpha]_D^{21}$ −49° (*c* 1·9 in EtOH) (Found: C, 63·6; H, 7·9. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·8%).

The mother-liquors from which acid (B) had separated were allowed to evaporate slowly; acid (A) was deposited in a *hydrated form*, m. p. 110—140°, $[\alpha]_D$ −105° (Found: C, 62·6; H, 7·8. $C_{15}H_{26}O_4,1{\cdot}5H_2O$ requires C, 61·8; H, 7·8%). Refluxing for 2 hr. with benzene in a Dean and Stark apparatus gave a white powder, m. p. 160°. Crystallisation from ethyl acetate gave ***lumi*-11β(H)-*santoninic acid*** (IIIβ), $\lambda_{max.}$ 2440, 3350 (log ε 3·75 and 2·38), $\nu_{max.}$ 3550, 1698, 1658, and 1580 cm.$^{-1}$ (in Nujol) (Found: C, 68·2; H, 7·6%; equiv., 289. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%; equiv., 264). Its **2 : 4-*dinitrophenylhydrazone*** consisted of deep orange needles (from ethanol), m. p. 259—260°, $\lambda_{max.}$ 2220, 2580, (2850), 3830 Å (log ε 4·12, 4·15, 3·94, 4·54) (Found: C, 56·8; H, 5·4. $C_{21}H_{24}O_7N_4$ requires C, 56·8; H, 5·4%).

Lumi-11β(H)-*santonin*.—(*a*) The acid A (0·5 g.) in ethanol (10 c.c.), treated with diazomethane, gave the ***lactone*** (IVβ) (0·4 g.) which crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 125°, $[\alpha]_D$ −112° (*c* 1·46 in MeOH), $\lambda_{max.}$ 2380 and 3400 Å (log ε 3·66 and 2·41), $\nu_{max.}$ 1780, 1689, and 1585 cm.$^{-1}$ (in Nujol) (Found: C, 73·2; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). (*b*) The lactone (0·3 g.) was obtained when the acid (0·5 g.) was heated on the water-bath with acetic anhydride (5 c.c.).

Reduction of Lumi-11β(H)-*santoninic Acid* (IIIβ).—The acid (0·5 g.) in ethyl acetate (100 c.c.) was reduced over Adams catalyst (0·2 g.) at 1 atm. of hydrogen. *Dihydrolumi*-11β(H)-***santoninic acid*** (Vβ) (0·45 g.) was obtained and crystallised from ethyl acetate as prisms, m. p. 150°, $[\alpha]_D$ −88° (*c* 1·4 in MeOH), $\lambda_{max.}$ 2830 Å (log ε 1·95), log ε 3·73 at 2200 Å (not a max.), $\nu_{max.}$ 1713 cm.$^{-1}$ (Found: C, 63·7; H, 8·2. $C_{15}H_{22}O_4,H_2O$ requires C, 63·4; H, 8·5%). This gave a **2 : 4-*dinitrophenylhydrazone***, scarlet needles (from ethanol), m. p. 226° (Found: C, 57·8; H, 5·4. $C_{21}H_{26}O_7N_4$ requires C, 56·5; H, 5·8%).

Dihydrolumi-11β(H)-***santonin*** (VIβ).—(*a*) Lumi-11β(H)-santonin (IVβ) (0·2 g.) in ethyl acetate (25 c.c.) was reduced over Adams catalyst (20 mg.), giving a solid (0·15 g.), m. p. 171·5—172·5°. Crystallisation from ethyl acetate–light petroleum (b. p. 40—60°) gave the desired ***lactone*** as prisms, m. p. 173° (Found: C, 72·8; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%). (*b*) Dihydrolumi-11β(H)-santoninic acid (Vβ) (1 g.) was treated in methanol with ethereal diazomethane, giving the lactone (VIβ) (0·9 g.), m. p. 172° (from ethyl acetate–light petroleum), $\lambda_{max.}$ 2850 (log ε 1·89), log ε 3·7 at 2200 Å (not a max), $\nu_{max.}$ 1780, 1720 cm.$^{-1}$ (Found: C, 72·6; H, 7·7%).

Reduction of Dihydrolumi-11β(H)-*santoninic Acid* (Vβ) *with Potassium Borohydride*.—A solution of the acid (0·2 g.) in 0·05N-sodium hydroxide (20 c.c.) containing potassium borohydride (0·2 g.) was set aside for 36 hr. It was acidified and extracted with chloroform, from which a gum was obtained. Trituration with light petroleum gave a solid (0·15 g.), m. p. 108—110°, which on crystallisation from light petroleum gave the required ***lactone*** (VIIβ) as needles, m. p. 114° (Found: C, 72·0; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

Isomerisation of Lumi-11β(H)-*santonin* (IVβ).—A stream of hydrogen chloride was passed for 4 hr. into a solution of the lactone (1·8 g.) in chloroform (100 c.c.), and the solution was set aside for 12 hr., then washed with water and dried. The gum produced when the solution was evaporated was dissolved in ethyl acetate–light petroleum (b. p. 40—60°) and set aside. The ***chloro-lactone*** (XX) (1·3 g.) was deposited as prisms, m. p. 130—135°. After chromatography on neutral alumina with light petroleum–benzene it had m. p. 139—140°. Crystallisation from ethyl acetate–ligroin gave prisms, m. p. 139—140°, $[\alpha]_D$ −182° (*c* 1·44 in MeOH), $\lambda_{max.}$ 2215 (log ε 3·93) and 3320 Å (log ε 1·8), $\nu_{max.}$ 1775, 1707 (*cyclo*pentenone), 1600 cm.$^{-1}$ (in $CHCl_3$) (Found: C, 64·1; H, 6·7. $C_{15}H_{19}O_3Cl$ requires C, 63·7; H, 6·7%).

Reduction of the Lactone (XX). **4-*Chloro*-2-*oxoguaian*-8 : 13-*olide*** (XVIβ).—The preceding compound (XX) (0·15 g.) in ethyl acetate (50 c.c.) was hydrogenated over Adams catalyst (50 mg.). The ***product*** (0·15 g.), isolated in the usual way, had m. p. 167—168°. Two crystallisations from ethyl acetate–light petroleum gave needles, m. p. 191—192°, $\lambda_{max.}$ 2980 (log ε 1·54), $\nu_{max.}$ 1770, 1740 cm.$^{-1}$ (in $CHCl_3$) (Found: C, 63·6; H, 7·5. $C_{15}H_{21}O_3Cl$ requires C, 63·3; H, 7·4%).

Dehydrochlorination of the Lactone (XX). **2-*Oxoguai*-1(15) : 4-*dien*-8 : 13-*olide*** (XXIβ).—The chloro-compound (XX) (0·3 g.) was refluxed with fused sodium acetate (0·35 g.) in dry ethanol (15 c.c.) for 7 hr., then set aside overnight. The ethanol was removed, the residue was

extracted with ethyl acetate, and the extract washed with water, dried, partly evaporated, and diluted with light petroleum. The *diene* was then obtained as rods (70 mg.), m. p. 114—116°. Crystallisation from ethyl acetate–light petroleum raised the m. p. to 117—118° (Found: C, 73·1; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

Isomerisation of Dihydrolumi-11β(H)-santonin (VIβ).—The lactone (0·9 g.) in chloroform (100 c.c.) was treated as described previously, affording a gum, which dissolved in ethyl acetate–light petroleum. The *guiaenolide* (XIXβ) (0·36 g.), m. p. 142—170°, was gradually deposited. Crystallisation from ethyl acetate–light petroleum gave needles, m. p. 181°, $\lambda_{max.}$ 2840 Å (log ε 1·67), log ε 2·9 at 2140 Å (no max.) (Found: C, 72·8; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%). Ozonolysis of this product (XIXβ) gave a gum whose infrared spectrum showed maxima at 2750 (aldehyde), 1780 (lactone), 1748 (*cyclo*pentanone), 1727 (aldehyde), 1704 (ketone), and 1356 cm.$^{-1}$ ($CO{\cdot}CH_3$).

Dehydrogenation of the Acid (Vβ).—The acid was reduced with potassium borohydride as described above. The lactone (VII) (0·25 g.) was heated with 10% palladised charcoal (0·25 g.) for 14 min. at 300—320°. The product was extracted several times with light petroleum, and the combined extracts from three experiments were reduced to 4 c.c. This residue was then chromatographed on a 6 cm. column of neutral alumina. 7-Ethyl-1-methylnaphthalene (100 mg.) was obtained and characterised as its picrate and by means of its ultraviolet and infrared spectra.

Methyl 3 : 6-*Dioxoeudesm*-7(11)-*en*-13-*oate* (XXII; R = Me).—The acid (XXII; R = H) (100 mg.) in methanol (10 c.c.) was treated with excess of diazomethane in ether. After 30 min. the solvents were removed, giving the *ester* (100 mg.), which crystallised from ethyl acetate–light petroleum as needles, m. p. 121—121·5°, $\lambda_{max.}$ 2150 (2900), and 3300 (log ε 4·12, 1·68, and 1·42), $\nu_{max.}$ 1727 (αβ-unsaturated ester), 1710 (C:O), 1680 (αβ-unsaturated ketone), 1646 cm.$^{-1}$ (C=C) (Found: C, 68·8; H, 7·8. $C_{16}H_{22}O_4$ requires C, 69·1; H, 7·9%).

3-*Oxoeudesma*-4 : 7(11)-*dien*-6 : 13-*olide* (XXIV).—The acid (XXII; R = H) (0·48 g.) was heated with acetic anhydride (5 c.c.) for 7 hr. and the mixture was then evaporated to dryness in a vacuum. The residual oil was chromatographed in ethyl acetate–light petroleum on neutral alumina. Elution with benzene–light petroleum (3 : 2) gave a colourless gum which rapidly solidified. Crystallisation from ethyl acetate–light petroleum gave the *lactone* (7 mg.) as needles, m. p. 135° (Found: C, 73·3; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

3 : 6-*Dioxoeudesman*-13-*oic Acid* (XXIII; R = H).—The acid (XXII; R = H) (0·63 g.) in ethyl acetate (30 c.c.) was stirred overnight with Adams catalyst (70 mg.) in hydrogen. After filtration and removal of solvent 3 : 6-*dioxoeudesman*-13-*oic acid* (0·3 g.), m. p. 171—172·5°, was obtained, which crystallised from methanol as needles (0·23 g.), m. p. 176—177°, $[\alpha]_D^{18}$ −25° (*c* 1·3 in MeOH) (Found: C, 63·7; H, 8·2. $C_{15}H_{22}O_4,H_2O$ requires C, 63·4; H, 8·5%). Its *methyl ester* (XXIII; R = Me) crystallised from ethyl acetate–light petroleum as rods, m. p. 124°, $[\alpha]_D^{17}$ −37° (*c* 1·59 in MeOH) (Found: C, 69·1; H, 8·7; OMe, 10·9. $C_{16}H_{24}O_4$ requires C, 68·6; H, 8·6; OMe, 11·1%). The ester affords the acid when kept with 5% methanolic potassium hydroxide. The *monoxime* of the ester crystallised from methanol as needles, m. p. 162—163° (Found: N, 4·8; OMe, 10·5. $C_{16}H_{25}O_4N$ requires N, 4·7; OMe, 10·5%).

3-*Hydroxyeudesman*-6 : 13-*olide* (XXVI).—A solution of 3 : 6-dioxoeudesman-13-oic acid (0·4 g.) in methanol (20 c.c.) and water (20 c.c.) containing a slight excess of potassium hydroxide and potassium borohydride (0·5 g.) was set aside for 3 days, then acidified and extracted with ethyl acetate. The extract was washed with sodium carbonate solution and dried. The required *lactone* (0·17 g.) was obtained having m. p. 147—149° and crystallised from ethyl acetate–light petroleum as needles, m. p. 149—151°, $[\alpha]_D^{19}$ +52° (*c* 1·4 in $CHCl_3$) (Found: C, 71·5; H, 9·7%; equiv., 240. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%; equiv., 252).

Eudesm-3-*en*-6 : 13-*olide* (XXVII).—The preceding compound (100 mg.), dissolved in phosphorus oxychloride (0·5 c.c.) and pyridine (5 c.c.), was set aside for 24 hr. The *product* (50 mg.) crystallised from aqueous ethanol as needles, m. p. 93—94° (Found: C, 77·1; H, 9·4. $C_{15}H_{22}O_3$ requires C, 76·9; H, 9·5%). Ozonolysis of this product followed by reduction of the ozonide over palladised charcoal gave a gum which with sodium hypoiodite gave iodoform and gave positive Tollens's and Schiff's tests.

Dehydrogenation of 3-*Hydroxyeudesman*-6 : 13-*olide* (XXVI).—The lactone (2·5 g.), as a gum obtained from the potassium borohydride reduction, was heated at 295° for 19 hr. with 10% palladised charcoal in a stream of nitrogen. The product was extracted with light petroleum, and the extract filtered, reduced to 20 c.c., and passed through a 4″ column of neutral alumina.

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The eluate, on removal of solvent, gave a colourless oil (0·4 g.) indistinguishable in spectrum from 7-ethyl-1-methylnaphthalene, $\lambda_{max.}$ 2285, 2820 (3200 Å) (log ε 4·84, 3·68, and 2·45). Its picrate, m. p. 87°, did not depress the m. p. of authentic 7-ethyl-1-methylnaphthalene picrate. The alumina in the column was washed with 90% phosphoric acid (40 c.c.), and the acid was diluted with water to 150 c.c. and extracted with light petroleum, giving a blue extract having absorption maxima at 2850 (3250) Å (log ε 4·65 and 4·22). A second dehydrogenation of the pure lactone (XXVI) (390 mg.) afforded 7-ethyl-1-methylnaphthalene (170 mg.) whose picrate had m. p. and mixed m. p. 90—91°. No azulene-like compound was observed in this experiment.

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UNIVERSITY CHEMICAL LABORATORY,
TRINITY COLLEGE, DUBLIN.

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680. *Behaviour of Some Alkylphosphonic Acids in Paper Chromatography and Paper Electrophoresis.*

By GENNADY M. KOSOLAPOFF and CLARENCE H. ROY.

The migration rates of several lower alkylphosphonic acids were determined by paper chromatography and paper electrophoresis. The variation of migration rate with the size of the alkyl group permits location but not separation of the acids.

MANY of the methods commonly used of synthesis of alkylphosphonic acids require as final step the separation of inorganic acids of phosphorus from the phosphonic acids. In some instances this separation is tedious and often can be accomplished only by fractional distillation of some derivative of the phosphonic acid. At the same time very little is known about the behaviour of mixtures of alkylphosphonic acids with the result that in some syntheses, particularly those using aluminium chloride as catalyst, one is uncertain of the isomeric identity or purity of the final product. For control of these factors, paper-chromatographic and -electrophoretic means of identification and, possibly, purification, of alkylphosphonic acids were examined. When this work was commenced, no data on true organophosphorus acids existed, but since then Weil [1] reported his results on chromatographic migration rates, on paper, of some aromatic phosphonic acids. In view of our primary interest, at that time, in the aliphatic unsubstituted phosphonic acids, chromatography or electrophoresis necessitated finding means of detection of small amounts of these acids on paper. Since alkylphosphonic acids are stable and no coloured derivatives are known, possibilities were limited. After preliminary experimentation, we found it most convenient to use direct indicator application or formation of an insoluble salt, particularly that of lead. For alkylphosphonic acids Weil's methods did not give such clean location of the spots as ours, which permitted location of as little as 0·01 mg. on the paper.

With butan-1-ol, equilibrated with water, as the mobile phase in ascending paper strip chromatograms, the higher ($>C_{10}$) alkylphosphonic acids migrated totally with the advancing solvent front, as also did the lower dialkylphosphinic acids. Addition of up to 10% of pyridine or acetic acid to the solvent failed to change the mode of advance of these acids, as was to be expected from the very low solubility of the higher alkylphosphonic acids in the aqueous phase. The annexed Table lists R_F values for the lower alkylphosphonic acids, established by runs of seven hours at 30—31° with water-saturated butanol alone. It shows that the approximate trend toward higher R_F values in a homologous series of alkylphosphonic acids has many and large exceptions, the two most remarkable

[1] Weil, *Helv. Chim. Acta*, 1955, **38**, 1274.

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being the high R_F values of the propyl and the butyl members, indicating a higher lipophilic character of these acids than would have been expected from their position in the series. Branching tends to reduce the R_F values, owing probably to steric effects at least to some extent. The variation of the R_F cannot be directly related to the steady variation of acidic dissociation constants which were reported from this Laboratory a few years ago.[2]

Alkylphosphonic acids.

Alkyl	Me	Et	Pr^n	Bu^n	n-C_5H_{11}	n-C_6H_{13}	Pr^i	Bu^i	Bu^s	Bu^t
R_F	0·54	0·51	0·80	0·81	0·62	0·74	0·78	0·54	0·72	0·38
Migration (mm.)...	113	107	100	107	99	96	107	97	100	97

For electrophoresis of alkylphosphonic acids on paper strips, the findings may be summarized as follows. If the acids are made to migrate along a paper strip which is in flat contact with the table of the apparatus, the bands of the migrating acids show convex fronts, but a suspended paper strip in which the migrating acid is allowed to come in contact only with the paper strip yields bands which have sharp flat fronts which can be readily measured. In an acidic medium (acetate buffer, pH 5·2) on Whatman No. 1 paper (also used for the chromatographic work) strips, the Reco electrophoresis apparatus being used, the migrations in one hour with 500 v were as in the Table (the actual physical distance between the two electrolyte cell liquid surfaces was 50 cm.; hence the values of field strength in v cm.$^{-1}$ can be readily obtained). The results indicate a rather narrow total band of migration distances for the group as a whole, without any satisfactory order within it. Runs in which the time was varied from 1 to >7 hr. gave similar results.

A comparison of the methods of suspension of the paper strips is shown in the following Table. The duration, as above, is 1 hr., the total applied voltage being 700 v.

Distances migrated (mm.)

	Me	Et	Pr^n	Bu^n	Pr^i	Bu^t
Paper flat	121	131	99	110	98	95
Paper suspended	136	131	125	132	130	125

Attempts to obtain a better spread of migration distances by the use of lower and higher voltages were unsuccessful. Even less satisfactory were the results with basic media, borax–sodium hydroxide buffer with pH 10·8, and borax buffer with pH 9·3. Not only were the bands of the acids quite diffuse and difficult to delineate, but they were accompanied by diffuse slow-moving bands which tended to obscure the picture. Evidently these secondary bands were produced by partially and completely dissociated units, since they were not apparent in acidic media and were weaker in the pH 10·8 buffer than in the pH 9·3 buffer.

While paper chromatography and electrophoresis on paper yields locatable spots of various lower alkylphosphonic acids, the spread of the migration values is small and irregular, making these methods rather unsuitable for separation of mixtures, although they may be used for identification of individual acids. The electrophoretic method failed to cause any motion of the higher alkylphosphonic acids even with the highest potential (750 v) under all conditions tried, including both acidic and alkaline media.

Experimental

The phosphonic acids were prepared by conventional methods.[2]

Paper chromatography was done in a large bell jar with one-inch wide strips of Whatman No. 1 paper for ascending chromatograms, and butan-1-ol saturated with water as the fluid. The acids were deposited by a micropipette on the strips in the form of one carefully measured drop located at the same distance from the level of the butanol in the tank. The acid was deposited in 0·1M-solution and the spotted paper was allowed to equilibrate suspended in the tank overnight.

The electrophoretic work was done with Reco Electrophoretic apparatus manufactured by

[2] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3379.

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Research Equipment Corp., of Oakland, California, U.S.A., as Model E-800-2. The acid samples were applied stripe-wise across the paper strips precisely 14 cm. from the centre-line of the apparatus, after the strips had been moistened with the desired buffer solution and excess of electrolyte removed by blotting, again with Whatman No. 1 paper. The application site was nearer to the cathode terminal.

With either technique it is undesirable to encircle the location of the initial spot or stripe by a pencil mark. Comparative runs, especially for paper chromatography, showed that encirclement with graphite (and probably owing to the compression of the paper) slows the motion of the phosphonic acid, *i.e.*, the pencilled circle retards or " captures " the substrate for an appreciable time, giving low values for extent of migration.

The following methods were found to be satisfactory for locating the alkylphosphonic acids on paper in amounts of 0·01 mg. or greater.

Indicator Method.—After being dried under a pair of infrared heat lamps, the strips were sprayed uniformly by means of a compressed air-atomiser with bromothymol-blue solution prepared as follows. To a solution of bromothymol-blue (0·20 g.) in acetone (200 ml.) and ether (200 ml.) were added distilled water (1 ml.) and potassium hydroxide (1 g.). The mixture was shaken vigorously and kept for several hours, during which the solution changed from yellow to deep blue. After several days, the mixture deposits a viscous aqueous phase. The supernatant solution is used for charging the atomizer, yielding a very stable colour which can be read very readily, with excellent blue–yellow contrast on the chromatograms.

A somewhat less satisfactory, although still usable, indicator solution is obtained by treatment of methyl-red in acetone with very concentrated aqueous potassium hydroxide. The red–yellow contrast produced by this indicator is also readily seen on the chromatogram.

Lead Salt Method.—Salts of copper and iron failed to give good results under a variety of conditions. The lead salts gave the best results. The paper strip was dipped briefly into a saturated solution of lead acetate, rinsed thoroughly in running tap water, and then dipped into, or sprayed with, a dilute solution of sodium sulphide or ammonium sulphide. The concentration of the sulphide solution was not critical. The location of the phosphonic acid is shown by a black spot on a light tan background.

Ross Chemical Laboratory, Alabama Polytechnic Institute,
Auburn, Alabama, U.S.A. [*Received, March 28th*, 1957.]

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681. *Polarographic Reduction Half-wave Potentials of Some Phosphonic Acids.*

By Gennady M. Kosolapoff and Charles J. Jenkins, tert.

Polarographic reduction half-wave potentials were determined for nine nitro-substituted phenylphosphonic acids. Polarographic reduction with a dropping-mercury electrode could not be effected for *o*- and *p*-bromo-, *o*-chloro-, or 3-amino-4-bromo-phenylphosphonic acid.

Much work has been reported on polarographic reduction of organic compounds on a dropping-mercury electrode, but none for organophosphorus compounds. An examination of this class of compound was warranted for theoretical reasons and because the data might be utilised for electrolytic syntheses.

The nearest analogue that has been subjected to polarographic reduction is *m*-nitrobenzenesulphonic acid;[1] in buffers ranging from acidic to pH 8 this acid yields one polarographic wave whose half-wave potential moves steadily to more negative values with increase of pH; at pH 8—12 it gives two waves, the first following the pattern set by the single wave described above, whilst the second wave tends to lower the negative magnitude of its half-wave potential with increase of pH. The data reported also indicated the irreversibility of the reduction both by the form of the curves and by the fractional electron requirement calculated by the conventional route.

[1] Korschunov, Vertyulina, and Malyergina, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 261.

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With this background, we felt that polarographic reduction of nitrophenylphosphonic acids should be possible and this proved justified. We expected that halogen-substituted phosphonic acid would also be reducible on a dropping-mercury electrode, for halogenobenzoic acids are; but it is known that halogenophenylphosphonic acids can be readily

TABLE 1. *Substituted phenylphosphonic acids.*

No.	Subst.	$-E_{1/2}$ (first wave) pH 2·3	pH 6·9	pH 10·0	$-E_{1/2}$ (second wave) pH 10·0
1	2-Br-4-NO_2	0·195	0·544	0·687	1·389
2	4-Cl-3-NO_2	0·126	0·638	0·738	—
3	4-HO-3-NO_2	0·211	0·604	0·750	1·571
4	4-MeO-3-NO_2	0·255	0·668	0·836	—
5	3-Br-2-NO_2	0·217	0·648	0·695	1·083
6	*o*-NO_2	0·206	0·549	0·73	0·91
7	*m*-NO_2	0·230	0·639	0·773	—
8	*p*-NO_2	0·244	0·629	0·747	1·483
9	4-Nitrobenzylphosphonic acid	0·254	0·557	0·782	1·60

dehalogenated by catalytic hydrogenation under mild conditions.[2] However, *o*- and *p*-bromo-, *o*-chloro-, and 3-amino-4-bromo-phenylphosphonic acid were not reduced on the dropping-mercury electrode in buffer solutions with pH 10 or pH 2·15. In these cases the curve was that obtained from the buffer alone. It is possible to rationalise this failure by regarding the electron-withdrawing effect of the phosphonic acid group as being sufficiently strong as to prevent the rupture of the carbon–halogen bond in any of the three isomeric positions in the phenyl ring.

The polarograms of the various nitrophenylphosphonic acids were obtained in each instance at pH 2·3, 6·9, and 10·0, in order to secure data for acidic, neutral, and basic media, and to compare the resulting values with the results secured for the nitrophenylsulphonic acid.[1] The results are in Table 1. It is evident that the polarographic reduction of these acids in neutral or acidic media results in a single polarographic wave. In alkaline media, however, six of the compounds showed a second polarographic reduction wave, whilst three showed but one wave. The trend of the values of the half-wave potential of the first wave with variation of pH is invariably toward increasing negative values of the reduction potential, which agrees with the results for the sulphonic acid analogue.[1] Nevertheless, it is curious that the *m*-nitrophenylphosphonic acid displayed but one reduction wave in alkaline media, unlike its sulphonic analogue which gave two.

The relative ease of reduction of the mononitrophenylphosphonic acids, varies with alteration of the pH of the medium: in acid the order of increasing difficulty is *o*-, *m*-, *p*-; in neutral solution it is *o*-, *p*-, *m*-; in alkaline solution it becomes *o*-, *p*-, *m*-. The results indicate the greater difficulty of polarographic reduction of the nitrophenylphosphonic acids in comparison with the nitrobenzoic acids.[3]

EXPERIMENTAL

The polarograms were taken by a manually operated polarograph (Fisher Elecdropode), with the polarographic cell immersed in a thermostat at 25·0° ± 0·01°.

The phosphonic acids, prepared by conventional methods, were reduced in 0·002M-solutions containing 0·01% of gelatin for the (at least partial) suppression of maxima. Lower concentrations of gelatin were tried without success. We also failed to suppress maxima by employing a rotating "hoe."[4]

The buffer solutions consisted of citric acid–disodium hydrogen phosphate for pH 2·3, mono- and di-sodium phosphate for pH 6·9, and glycine–sodium chloride–sodium hydroxide or boric acid–potassium chloride–sodium hydroxide for pH 10·0. The decomposition potentials of these were, respectively, −0·80 v for pH 2·3, −1·5 v for pH 6·9, and −1·8 v for pH 10·0 (referred to a saturated calomel electrode).

[2] Freeman and Doak, *J. Org. Chem.*, 1956, **21**, 238.
[3] Kolthoff and Lingane, "Polarography," Interscience Publ., Inc., New York, 2nd edn., Vol. I, p. 754.
[4] Skobeta and Kavetskii, *Zavodskaya Lab.*, 1949, **15**, 1299.

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The capillary characteristics were:

Drop time (sec. per drop)	2·992	3·135	3·260	3·363	3·540	3·694	3·880	4·097
Capillary const. ($C = m^{2/3}t^{1/6}$)	2·277	2·222	2·179	2·141	2·096	2·046	1·996	1·936

Table 2 lists the values of the diffusion current, as microamp. The second wave obtained for six of the acids in alkaline solution was too diffuse in its appearance to permit a reasonable estimate of the diffusion current. The numbering of the acids in Table 2 corresponds to that in Table 1.

TABLE 2.

No.	pH 2·3	6·9	10·0	10·0 (second wave)	No.	pH 2·3	6·9	10·0	10·0 (second wave)
1	5·61	3·53	1·4	—	6	5·73	5·49	2·5	3
2	5·31	4·37	1·3	—	7	6·30	4·21	1·3	—
3	5·64	3·47	0·22	5	8	5·81	3·38	1·3	3
4	5·61	3·38	1·2	—	9	5·98	4·42	2·1	3
5	5·60	4·30	1·9	2					

The solutions used were freshly prepared and the pH of each was checked potentiometrically before use. It was noted that the solutions of the nitrophenylphosphonic acids in the above buffers, with added gelatin, readily develop bacterial cultures in contact with air for >1 day under local conditions.

The estimation of the half-wave potentials was performed graphically by determination of half the ordinate distance between the initial and the final current–voltage curves. Some of the half-wave potentials were also estimated by differential plotting. The results agreed with each other well within 0·003 v.

Ross CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE,
AUBURN, ALABAMA, U.S.A. [*Received, March 28th*, 1957.]

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682. α-1 : 4-*Glucosans. Part VI.* Further Studies on the Molecular Structures of Glycogens.*

By A. MARGARET LIDDLE and D. J. MANNERS.

Twenty-five samples of glycogen, with average chain lengths ranging from 8 to 18 glucose residues, have been degraded by barley β-amylase. The percentage conversions into maltose were 46 ± 7 in all but two instances. *Cardium* glycogen and one sample of rabbit liver glycogen had unusually low β-amylolysis limits of 14 and 25% respectively. These results illustrate the variation in molecular structure which can exist in glycogens.

The highly branched nature of the interior of several glycogens has been confirmed by α-amylolysis.

The use of acetic acid in the purification of glycogen is discussed.

OUR earlier studies [1,2] indicated differences in the degree and position of branching among (*a*) glycogens from different biological sources, and (*b*) different glycogen samples from the same source. These observations are extended in the present paper, which reports structural analyses of several additional glycogens by periodate oxidation, and by the use of β- and α-amylase. A preliminary account of part of this work has been published.[3]

Twenty-five samples of glycogen have been analysed. A number of these were kindly provided by Drs. D. J. Bell and G. R. Tristram and the determination of certain chain lengths ($\overline{CL}$) has already been reported.[4] The remainder were isolated by extraction of the tissues with hot water or 30% potassium hydroxide (Pflüger method) and purified by

* Part V, *J.*, 1957, 2205.

[1] For review, see Manners, *Adv. Carbohydrate Chem.*, 1957, **12**, 261.
[2] Bell and Manners, *J.*, 1952, 3641.
[3] Liddle and Manners, *Biochem. J.*, 1955, **61**, xii.
[4] Manners and Archibald, *J.*, 1957, 2205.

precipitation first from 80% acetic acid and then from ethanol.[5] The polysaccharides had glucose contents of 94—97%, specific rotations (in water) of 191° to 201°, and the glycogen–iodine complexes showed maximum absorption at 420—470 mμ. Average chain lengths were determined by measurement of the maximum amount of formic acid liberated by potassium metaperiodate oxidation at room temperature. This method of analysis gives reproducible results which are in agreement with enzymic or methylation analyses of the *same* samples.[2,4]

The glycogens were incubated with barley β-amylase, at pH 4·6 and 35°, and the percentage conversions into maltose determined (see Table 1). The enzyme preparation was free from maltase and α-amylase, but contained Z-enzyme [6] and showed slight hydrolytic activity towards maltotriose. The hydrolytic activities due to Z-enzyme and that towards maltotriose are not significant, since Z-enzyme does not affect the β-amylolysis of glycogens, and maltotriose is not a product of enzyme action.

Peat, Whelan, and Thomas [7] have shown that the side chains in an amylopectin β-limit dextrin contain 2 or 3 glucose residues, whilst Summer and French,[8] from a study of the

TABLE 1. *The action of barley β-amylase on some glycogens.*

Sample no.	Source of glycogen	$\overline{CL}$ [a]	β-Amylolysis limit (%)	Exterior [b] chain length	Interior [c] chain length
1	*Arenicola*	11	43	7—8	2—3
2	*Cardium*	8	14	3—4	3—4
3	Cat liver IV	13[4]	53 [d]	9—10	2—3
4	,, VI	12[4]	52 [d]	8—9	2—3
5	Cock liver	13	39	7—8	4—5
6	Fœtal pig liver	11[4]	49	8	2
7	Fœtal sheep liver (alkali-treated) [e]	13[2]	49	9	3
8	Human muscle II	11	40	7	3
9	*Mytilus edulis* IV	12[4]	51	8—9	2—3
10	,, V	9[4]	40	6	2
11	,, VI	13[4]	46	8—9	3—4
12	,, VII	13	46	8—9	3—4
13	,, VIII	13	45	8—9	3—4
14	,, IX	10	51	7—8	1—2
15	,, X	14	45	8—9	4—5
16	Rabbit liver I	13	25	5—6	6—7
17	,, III	13[4]	51	9	3
18	,, IV	13[4]	45	8—9	3—4
19	,, V	14[4]	51	9—10	3—4
20	,, VI	18[9]	52	12	5
21	,, X	12[4]	49	8—9	2—3
22	,, XII	17	43	9—10	6—7
23	,, XIII	15	46	9—10	4—5
24	Rabbit muscle II	11	39	6—7	3—4
25	Skate liver	13	45	8—9	3—4

[a] Superscript numbers refer to chain-length determination reported in refs. 2, 4, or 9. [b] No. of glucose residues removed by β-amylase + 2·5. [c] $\overline{CL}$ − exterior chain length − 1. [d] Incubation with crystalline sweet-potato β-amylase gave β-amylolysis limits of 54 and 52% respectively. [e] Before alkali treatment, this glycogen had a β-amylolysis limit of 49%.[2]

action of β-amylase on model substrates, concluded that the exterior chain "stubs" in a glycogen or amylopectin β-limit dextrin "would never be any shorter than 2·5 glucose units." The exterior and interior chain lengths reported in Table 1 have therefore been calculated on the assumption that β-amylase action on glycogen ceased at the second or third glucose residue from the outermost branch points.

[5] Bell and Young, *Biochem. J.*, 1934, **28**, 882.
[6] Peat, Thomas, and Whelan, *J.*, 1952, 722.
[7] Peat, Whelan, and Thomas, *J.*, 1952, 4546.
[8] Summer and French, *J. Biol. Chem.*, 1956, **222**, 469.
[9] Haworth, Hirst, and Isherwood, *J.*, 1937, 577.

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It has been suggested [10] that purification of glycogens by precipitation with acetic acid renders them less susceptible to degradation by the enzymes muscle phosphorylase and amylo-1 : 6-glucosidase. After treatment with hot alkali, the glycogens could then be completely degraded by these enzymes. Fœtal sheep liver glycogen, purified by the acetic acid method, has therefore been digested with 0·1N-sodium hydroxide at 100° for 30 min. This treatment did not increase the β-amylolysis limit. Further, four precipitations of rabbit liver or yeast glycogen from 80% acetic acid, followed by an ethanol precipitation, did not decrease the β-amylolysis limits. We conclude that the purification of glycogen with acetic acid does not affect the extent of degradation by β-amylase.

The above results clearly demonstrate the variation in branching characteristics which exist in glycogens, and in particular, the structural differences in samples from the same biological source. Thus, $\overline{CL}$ values for rabbit liver glycogen range from 12 to 18, whilst glycogens (samples 16, 17, 18) with the same chain length differ in position of branching in the constituent chains. Rabbit liver I glycogen is unusual in that both the exterior and interior chains contain *ca.* 6 glucose residues; normally, the exterior chains are roughly twice the length of the interior chains. The presence of relatively short chains in rabbit liver I glycogen has been confirmed, since the extent of degradation by muscle and potato phosphorylase was abnormally low.[11]

Glycogens from *Arenicola* (lug worm), cock liver, and *Cardium* (cockle) do not appear to have been examined previously. The first two samples have normal structures, but the *Cardium* glycogen has unusually short exterior chains (3—4 glucose residues) although the interior chains are of normal length.

The action of purified salivary α-amylase on a number of glycogen-type polysaccharides has also been investigated. Although α-amylases catalyse random hydrolysis of α-1 : 4-glucosidic linkages in these polysaccharides, the extent of degradation should be related

TABLE 2. *The α-amylolysis of some branched α-1 : 4-glucosans.*

Source of polysaccharide	Percentage of α-1 : 6-glucosidic linkages	Apparent % conversion into maltose (P_M) * 2 hr.	6 hr.	24 hr.
Glycogens :				
Arenicola	9	56	71	76
Cardium	13	39	49	54
Cock liver	8	57	72	76
Helix pomatia	14	51	64	67
Mytilus edulis VII	8	60	73	80
,, VIII	8	61	76	80
,, IX	10	62	78	83
,, X	7	61	75	80
Skate liver	8	59	75	80
Amylopectin :				
Waxy maize starch	5	78	93	95
β-Limit dextrins : †				
Helix pomatia glycogen	22	21	26	29
Waxy maize starch	10	48	59	66

* All digests contained 4·6 units of α-amylase per mg. polysaccharide (see p. 3436).

† Prepared by the prolonged action of β-amylase on the polysaccharide, removal of maltose by dialysis, and isolation by freeze-drying.

to the proportion of α-1 : 6-glucosidic linkages present, since these linkages and certain adjacent α-1 : 4-glucosidic linkages resist enzymic action.[12] Several polysaccharides were therefore incubated (at pH 7·0 and 35°) with salivary α-amylase, and the apparent percentage conversion into maltose (P_M) determined at intervals (see Table 2). Paper chromatography showed that extensive random hydrolysis had occurred, the products being glucose,

[10] Illingworth, Larner, and Cori, *J. Biol. Chem.*, 1952, **199**, 631.
[11] Liddle, Ph.D. Thesis, Edinburgh, 1956.
[12] Whelan and Roberts, *Nature*, 1952, **170**, 748.

maltose, maltotriose (trace), and oligosaccharides with R_G 0·10, 0·05, and lower chromatographic mobilities.

Since the relative proportion of enzyme and substrate was constant, the variation in P_M values must reflect differences in molecular structure. In general, the extent of α-amylolysis appears to be inversely proportional to the degree of branching in the substrate. The low P_M values for *Helix pomatia* [2] and *Cardium* glycogens are in accord with the earlier evidence for compact and highly branched structures. Conversely, waxy maize starch and its β-limit dextrin have relatively open interior structures, since *ca.* 47 and 33% of the glucosidic linkages in the molecules can be hydrolysed by α-amylase.

Peat, Roberts, and Whelan [13, 12] reported that the products of α-amylolysis of a sample of rabbit liver glycogen included *ca.* 5% of maltulose and small quantities of fructose-containing α-dextrins, suggesting that fructose was a minor component of the glycogen. Examination of our α-amylase digests by paper chromatography with the orcinol spray reagent [14] or the acid resorcinol reagent [15] failed to show the presence of ketoses. It is concluded that fructose is not a constituent of the above glycogens.

Experimental

Preparation of Glycogens.—We are indebted to Dr. D. J. Bell for glycogen samples 7, 8, 16, and 17 and the cock liver tissue, and to Dr. G. R. Tristram who provided samples 14 and 15 and many of the animal tissues. The isolation and certain properties of these glycogens are recorded in Table 3. The yield varied from 0·3 to 1·6 g. per 100 g. of wet tissue, and the polysaccharides

Table 3. *The preparation and properties of some glycogens.*

Source of glycogen	Method of isoln.[a]	Method of purifn.[b]	$[\alpha]_D$, H_2O	$\lambda_{max.}$ of iodine complex (mμ) [c]
Arenicola	P	A	+200°	420
Cardium	W	PA	+201	420
Cock liver	W	PA	+191	440
Human muscle	P	A	+195	—
Mytilus edulis VII.....	W	PA	+200	420
,, VIII.....	W	PA	+194	420
,, IX.....	W	PA	+196	—
,, X.....	W	PA	+199	—
Rabbit liver XII.....	W	A	+193	470
,, XIII.....	W	A	+199	470
Rabbit muscle II.....	P	A	+194	—
Skate liver	P	A	+196	420

[a] P = Pflüger method; W = hot-water extraction. [b] A = precipitated with acetic acid and ethanol; PA = deproteinised with picric acid, then as A. [c] Determined as by Peat, Whelan, Hobson, and Thomas (*J.*, 1954, 4440) and corrected for light scattering.

had glucose contents of 94—97% (paper chromatography, and Shaffer–Somogyi estimation [16] after hydrolysis with 1·5N-sulphuric acid for 2 hr. at 100°).

Potassium Metaperiodate Oxidation of Glycogens.—The method was similar to that previously described,[2,4] the formic acid being titrated potentiometrically to pH 5·7 with carbonate-free [17] 0·01N-sodium hydroxide.

β-*Amylolysis of Glycogens.*—Barley β-amylase, from the Wallerstein Laboratories, New York, had an activity of 118 units/mg. by Hobson, Whelan, and Peat's method.[18] The enzyme preparation had a negligible reducing power and showed no maltase activity. It was free from α-amylase since it did not reduce the iodine-staining power of amylopectin β-limit dextrin, or the molecular weight of glycogen β-limit dextrin.[19] On incubation with potato amylose at

[13] Peat, Roberts, and Whelan, *Biochem. J.*, 1952, **51**, xvii.
[14] Bevenue and Williams, *Arch. Biochem. Biophys.*, 1951, **34**, 225.
[15] See Bell, "Modern Methods of Plant Analysis," Vol. II, ed. Paech and Tracey, Springer-Verlag, 1955, p. 21.
[16] Shaffer and Somogyi, *J. Biol. Chem.*, 1933, **100**, 695.
[17] Davies and Nancollas, *Nature*, 1950, **165**, 237.
[18] Hobson, Whelan, and Peat, *J.*, 1950, 3566.
[19] Greenwood, Jones, and Manners, unpublished work.

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pH 3·6 and 4·6, 72% and 95% conversion respectively into maltose was observed. This indicates the presence of Z-enzyme in the barley preparation (compare ref. 6). Maltotriose was very slowly hydrolysed by high concentrations of the enzyme (86 units/mg. of maltotriose).

Enzyme digests contained 0·1M-acetate buffer of pH 4·6, and toluene, and were incubated at 35°. Preliminary experiments in which rabbit liver V glycogen was incubated with 40, 60, 80, and 100 units of β-amylase per mg. of glycogen showed that in every case enzyme action was virtually complete within 4 hr. and that on incubation for a further 44 hr. the conversion into maltose did not increase by more than 1%. β-Amylolysis limits were therefore determined, in duplicate, by incubating glycogen (1 mg./ml.) with β-amylase (40—50 units/mg. of glycogen) at pH 4·6 in a total volume of 50 ml. Samples (3 ml.) were analysed at intervals for maltose,[16] and the mean results obtained after 24 and 48 hr. are recorded in Table 1. Duplicate analyses were identical or differed by no more than 1%.

After 48 hours' incubation under the above conditions, the digests contained active β-amylase. Addition of 1 drop of digest to 1% starch solution (2 ml.) caused immediate liberation of reducing sugar. Further, the addition of fresh β-amylase after 48 hr. did not increase the maltose content of the digest.

Portions of the digests were examined by paper chromatography. Ethanol (2 vol.) was added to precipitate protein and polysaccharide, and the supernatant solutions were deionised with IR-4B(OH) and IR-120(H) ion exchange resins, and concentrated. The chromatograms, developed with a silver nitrate–sodium hydroxide reagent,[20] showed the present of maltose and no other sugar.

α-Amylolysis of Glycogens.—α-Amylase was prepared from human saliva by the method of Fischer and Stein [21] except that the final crystallisation stage was omitted, and the enzyme isolated by freeze-drying in 0·2M-citrate buffer (pH 7·0). The enzyme preparation, with an activity of 42 units/mg. by a modification of Fischer and Stein's method,[21] had a negligible reducing power, slowly hydrolysed maltotriose (27 units/mg. of substrate), and contained a trace of maltase activity (37 units/mg. of substrate).

Standard digests containing polysaccharide (*ca.* 50 mg.), 0·5% sodium chloride solution (10 ml.), α-amylase solution (*ca.* 230 units, 1 ml.), and distilled water to 100 ml. were incubated at 35°. Portions (5 ml.) were analysed at intervals, for reducing sugar (see Table 2). The small (*ca.* 2%) increase in reducing power of the digest with waxy maize starch between 6 and 24 hours' incubation showed the virtual absence of maltase activity under the above conditions (4·6 units α-amylase/mg. of substrate.)

After 48 hr. a 10 ml. sample was removed from each digest, boiled, concentrated, and examined by paper chromatography. The silver nitrate–sodium hydroxide reagent showed the presence of glucose, maltose (R_G 0·49), maltotriose (traces only), and higher oligosaccharides including sugars with R_G 0·10 and 0·05. When duplicate chromatograms were sprayed with an orcinol reagent,[14] as used by Roberts *et al.*,[12,13,22] neither maltulose nor ketose-containing oligosaccharides could be detected. An authentic sample of maltulose had R_G 0·48, and a mixture of glucose and fructose (97 : 3) gave a positive ketose reaction under similar conditions.

Portions (4 ml.) of the digests were also heated with resorcinol (0·45% in water; 2 ml.) and hydrochloric acid–glycerol reagent (5 ml.) at 100° for 15 min. and the solutions examined colorimetrically.[15] If the fructose content of the glycogens was only *ca.* 3% then each aliquot would contain *ca.* 60 μg. of ketose. Under the above conditions, 30 μg. of fructose could be detected, and the intensity of colour with this was greater than that with any of the samples from the α-amylase digests.

The authors are grateful to Professor E. L. Hirst, F.R.S., and Drs. D. J. Bell and G. R. Tristram for their interest in this work, to Mr. I. D. Fleming for experimental assistance, to the Rockefeller Foundation for a grant, and to the Department of Scientific and Industrial Research for a maintenance allowance (to A. M. L.).

Department of Chemistry, University of Edinburgh. [*Received, April 8th*, 1957.]

[20] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.
[21] Fischer and Stein, *Arch. Sci.*, 1954, **7**, 131.
[22] Roberts, Ph.D. Thesis, University College, North Wales (Bangor), 1953.

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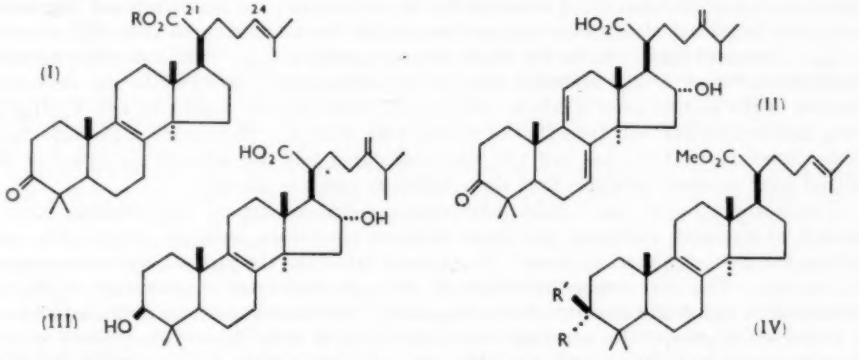
683. *The Chemistry of the Triterpenes and Related Compounds. Part XXXI.* The Isolation of Further Triterpene Acids from* Polyporus pinicola *Fr.*

By J. J. Beereboom, H. Fazakerley, and T. G. Halsall.

The examination of the triterpene constituents of *Polyporus pinicola* Fr. has been continued and two new acids have been isolated. The methyl ester monoacetate of one has been identified as methyl 3α-acetoxylanosta-8 : 24-dien-21-oate (IV; R = OAc, R′ = H). The other, which occurs along with its dehydro-derivative, is a dioxo-acid.

In Part XXVII [1] the isolation of methyl pinicolate A (methyl-3-oxolanosta-8 : 24-dien-21-oate) (I; R = Me) from triterpene constituents of *Polyporus pinicola* Fr. was described. Further investigation of the mixture of triterpenes present in the fungus has shown that it is very complex. Recent results of other workers support this view.

Shibamoto, Minami, and Tajima [2] have isolated from *P. pinicola* two acids, both described as $C_{30}H_{46}O_4$. One is a hydroxy-oxo-acid and the other a dihydroxy-acid. It is possible that the first is polyporenic acid C (II) [3-5] and the second tumulosic acid (III) [3, 6, 7]



although the agreement between the constants of the Japanese acids and those of polyporenic acid C and tumulosic acid is not good (see Experimental section). Polyporenic acid C is certainly present in *Polyporus pinicola* Fr.[8]

Schmid and Czerny [9, 10] have isolated an oxo-alcohol and three acids from *Polyporus pinicola*. The contents of the oxo-alcohol [9] (m. p. 116°; $[\alpha]_D$ +71°; $\lambda_{max.}$ 2360, 2450, and 2520 Å, ε 5400, 6000, and 4200) are in good agreement with those (m. p. 114—117°; $[\alpha]_D$ +68·5°; $\lambda_{max.}$ 2360 and 2430 Å, ε 4000 and 4500; inflexion: 2510 Å, ε 3000) of a mixture, as yet unresolved, of 21-hydroxylanosta-8 : 24-dien-3-one (75%) and the corresponding dehydro-derivative (25%) which has been isolated from the neutral portion of an extract of *Polyporus pinicola* Fr. by Guider, Halsall, and Jones.[11] The formulæ proposed by Schmid and Czerny [9, 10] for their three acids, I, II, and III are $C_{30}H_{48}O_3$, $C_{30}H_{48}O_3$, and

* Part XXX, *J.*, 1957, 753.

[1] Guider, Halsall, and Jones, *J.*, 1954, 4471.
[2] Shibamoto, Minami, and Tajima, *J. Japan. Forest Soc.*, 1953, **35**, 56.
[3] Cross, Eliot, Heilbron, and Jones, *J.*, 1940, 632.
[4] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.
[5] Bowers, Halsall, and Sayers, *J.*, 1954, 3070.
[6] Cort, Gascoigne, Holker, Ralph, Robertson, and Simes, *J.*, 1954, 3713.
[7] Guider, Halsall, Hodges, and Jones, *J.*, 1954, 3234.
[8] Fazakerley, Halsall, Jones, and Whitham, unpublished work.
[9] Schmid and Czerny, *Scientia Pharm.*, 1953, **21**, 258.
[10] *Idem*, *Monatsh.*, 1954, **85**, 1307.
[11] Guider, Halsall, and Jones, unpublished work.

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$C_{30}H_{48}O_4$. The constants are: I, m. p. 215—216°, $[\alpha]_D$ +50°; II, m. p. 196—198°, $[\alpha]_D$ +62°; and III, m. p. 265—267°. The constants of acid II suggested that it is pinicolic acid A (I; R = H) (m. p. 197—202°, $[\alpha]_D$ +68°); a specimen, kindly provided by Professor L. Schmid did not depress the m. p. of pinicolic acid A.

To simplify the separation of the triterpene constituents the fungus was first extracted with light petroleum. The extract was hydrolysed and the acidic and neutral fractions were separated. This paper is concerned with some of the constituents of the acidic fraction. The methyl esters from this fraction were separated by use of Girard's reagent T into two fractions called "light petroleum ketonic esters" and "light petroleum non-ketonic esters." This treatment does not necessarily separate all ketonic from non-ketonic esters as there may be present esters with oxo-groups (e.g., at $C_{(16)}$ in trimethyl-steroids) which do not react with Girard reagent T.

From the "light petroleum ketonic esters" methyl pinicolate A (I; R = Me) was isolated by chromatography on alumina along with a mixture of the methyl esters of a dioxo-acid (80%) and its dehydro-derivative (20%). The isolation of this type of mixture from wood-rotting fungi is quite common.[cf. 7, 12] The mixed esters had infrared bands at 1700 cm.$^{-1}$ indicative of a keto-group in a six-membered ring, and at 1723 cm.$^{-1}$ (very strong), indicative of both an ester group and a keto-group in a five-membered ring. A trimethyl-steroid skeleton being assumed for the dioxo-acid, the six-membered ring keto-group can be placed at $C_{(3)}$ since oxygen has, so far, been found in all trimethyl-steroids at $C_{(3)}$. The most likely site for the other carbonyl group is $C_{(16)}$. The molecular-rotation contribution[13, 4] of a $C_{(16)}$ carbonyl group is approximately −500°, whilst the molecular rotation of the methyl ester mixture ($[M]_D$ −217°, a molecular weight of 482 [$C_{31}H_{46}O_4$] being assumed) is 541° less than that of methyl pinicolate A. The nature of the side-chain of the dioxo-acid (cf. V) has not yet been elucidated but the infrared spectrum of the methyl ester mixture indicates that the vinylidene group is absent.

Chromatography of the "light petroleum non-ketonic esters" on alumina gave a number of fractions, including two main fractions containing hydroxy-esters. The first of these has been examined in detail. It was acetylated and the product chromatographed on alumina. The first compound obtained was a methyl ester monoacetate, $C_{33}H_{52}O_4$, containing no significant amount of diene impurity; its infrared spectrum indicated absence of a vinylidene group. Its constants were not identical with those of the known methyl 3β-acetoxylanosta-8 : 24-dien-21-oate (IV; R = H, R′ = OAc) ($[\alpha]_D$ +67°).[1] Instead, its low rotation ($[\alpha]_D$ +7°) suggested the presence of a 3α-acetoxy-group which is known to have a negative molecular-rotation contribution.[14] Proof that it was methyl 3α-acetoxylanosta-8 : 24-dien-21-oate (IV; R = OAc, R′ = H) was obtained by hydrolysing the acetoxy-group with methanolic potassium hydroxide at room temperature and then oxidising the hydrolysis product with chromic acid, methyl pinicolate A (methyl 3-oxo-lanosta-8 : 24-dien-21-oate) (I; R = Me) being obtained.

A second fraction (m. p. 142—144·5°; $[\alpha]_D$ +50·5°; showing no diene absorption) was shown by careful chromatography to be a mixture of two closely related methyl ester monoacetates which it was not possible to separate completely.

The preparation of methyl 3β-acetoxylanosta-7 : 9(11)-dien-21-oate, needed as a reference compound, is described.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform at room temperature. The alumina used for chromatography, unless otherwise stated, was Peter Spence Grade "H" which had been deactivated with 5% of 10% acetic acid. Light petroleum refers to the fraction with b. p. 60—80°. Ultraviolet spectra were determined in ethanol.

[13] Holker, Powell, Robertson, Simes, Wright, and Gascoigne, *J.*, 1953, 2422.
[13] Klyne, *J.*, 1952, 2916.
[14] Klyne and Stokes, *J.*, 1954, 1979.

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Extraction of Polyporus pinicola *Fr. with Light Petroleum.*—The air-dried fungus (1 kg.) was extracted five times with cold light petroleum (4 l. each) for 16 hr., and the extracts were combined and concentrated to a dark brown paste (81 g.). Further extraction gave negligible quantities of gum. The extract (80 g.) was heated under reflux with ethanol (90 c.c.), water (275 c.c.), and sodium hydroxide (50 g.) for 20 hr. The cooled solution was diluted with water and extracted with ether (10 × 200 c.c.) to yield the " light petroleum neutral fraction " (18·6 g.). The aqueous phase was acidified with hydrochloric acid and extracted with ether (5 × 250 c.c.) to yield the " light petroleum acidic fraction " (43 g.).

Methylation of the " Light Petroleum Acidic Fraction."—The acidic fraction (43 g.) in ether (400 c.c.) and acetone (10 c.c.) was treated with an excess of diazomethane in ether and kept overnight. The excess of diazomethane was then decomposed with acetic acid. The ethereal solution was decanted from a small amount of polymeric material, washed with 2N-sodium hydroxide solution and water, and dried. Evaporation gave a brown gum (42 g.). These esters (42 g.) in ethanol (400 c.c.), water (20 c.c.), and acetic acid (40 c.c.) were heated under reflux with Girard's reagent T (25 g.) for 1 hr. The cooled mixture was poured into ice-cold aqueous sodium carbonate (28·4 g.) and extracted with ether to yield the " light petroleum non-ketonic esters " (28 g.). The aqueous phase was acidified (Congo red) with concentrated hydrochloric acid and kept at 20° overnight. Extraction with ether then afforded the " light petroleum ketonic esters " (13 g.) as a pale yellow gum which deposited feathery needles.

Chromatography of the " Light Petroleum Ketonic Esters."—Chromatography of the " light petroleum ketonic esters " was carried out on Whatman No. 1 paper with a reversed phase system. The stationary phase was odourless kerosene [from a 20% (v/v) solution in ether], and the eluant was the lower phase of the system, propan-2-ol–water–odourless kerosene (7 : 3 : 1) by vol.).[15] The triterpenes were detected by treatment of the paper with antimony trichloride in acetic acid at 90° for 2 min. and then with the Noller reagent,[16] or by treatment with the Noller reagent alone. In this case two spots, R_f 0·39 and 0·73, were obtained. Methyl pinicolate A^1 gave a spot with R_f 0·39.

The esters (10·8 g.) were adsorbed from light petroleum–benzene (9 : 1; 200 c.c.) on alumina (1 kg.), deactivated with 10% of 10% aqueous acetic acid. Elution with light petroleum–benzene (1 : 1; 2500 c.c.) gave methyl pinicolate A^1 (methyl 3-oxolanost-8 : 24-dien-21-oate) (7·5 g.) which crystallised from methanol as needles, m. p. and mixed m. p. 119—121°, $[\alpha]_D$ +71° (Found: C, 79·4; H, 10·2. Calc. for $C_{31}H_{48}O_3$: C, 79·4; H, 10·3%). The ultraviolet absorption spectrum of the methyl pinicolate A indicated that it contained a small amount (3—4%) of methyl dehydropinicolate A [methyl 3-oxolanosta-7 : 9(11) : 24-trien-21-oate]. Light absorption: Max. 2430 and 2740 (broad) Å, ε 670 and 40. Inflexions, 2360 and 2520 Å, ε 690 and 450.

Further elution with light petroleum–benzene (2 : 3, 400 c.c.; 3 : 7, 800 c.c.) yielded a gum (1·8 g.) which from methanol gave the dimorphic *methyl ester* of a dioxo-acid, m. p. 128—130° (plates) and 133—136·5° (needles), $[\alpha]_D$ −45° (*c* 1·46) (Found: C, 77·4; H, 9·35. $C_{31}H_{46}O_4$ requires C, 77·15; H, 9·6. $C_{31}H_{44}O_4$ requires C, 77·45; H, 9·25. $C_{32}H_{46}O_4$ requires C, 77·35; H, 9·75. $C_{32}H_{44}O_4$ requires C, 77·7; H, 9·35%). The ultraviolet absorption spectrum indicated that the dioxo-ester contained about 20% of a 7 : 9(11)-dehydro-component. Light absorption: Max. 2350, 2430, and 2520 Å; ε 3400, 3600, and 2600 (M = 482 ≡ $C_{31}H_{46}O_4$ being assumed). Infrared absorption in Nujol; bands at 1723 (vs), 1700 (s), 1660 (w) (sh), and 810 (w) cm.$^{-1}$. Further elution with benzene and ether afforded a gum (1·5 g.) from which it was not possible to obtain any crystalline derivative.

Chromatography of the " Light Petroleum Non-ketonic Esters."—Paper chromatography of the esters (see above) gave a chromatogram having two spots with R_f values of 0·37 and 0·67. The former is probably due to traces of methyl pinicolate A not removed by separation with reagent.

The esters (9·4 g.) were adsorbed from light petroleum (100 c.c.) on alumina (1000 g.) deactivated with 10% of 10% aqueous acetic acid. Elution with the solvents indicated gave the following six fractions: (i) light petroleum–benzene (9 : 1, 1200 c.c.) (1·5 g.); (ii) light petroleum–benzene (8 : 2, 1200 c.c.) (0·3 g.); (iii) light petroleum–benzene (7 : 3, 750 c.c.; and 1 : 1, 750 c.c.) (1·1 g.); (iv) light petroleum–benzene (4 : 6, 600 c.c.) (0·5 g.); (v) light petroleum–benzene (3 : 7, 900 c.c.; and 1 : 9, 900 c.c.) (3·3 g.); (vi) benzene–ether and ether–methanol (1800 c.c.) (2·95 g.).

[15] Mills and Werner, *J.*, 1955, 3132.
[16] Noller, Smith, Harris, and Walker, *J. Amer. Chem. Soc.*, 1942, **64**, 3047.

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Further chromatography and infrared examination showed fraction (i) to be very probably a mixture of fatty acid esters. Fraction (iii) gave only gums on rechromatography.

The infrared spectra of fractions (iv)—(vi) had bands due to hydroxyl groups. Fraction (v) was adsorbed from light petroleum–benzene (4 : 1, 50 c.c.) on alumina (350 g.). Elution with light petroleum–benzene (1 : 1, 300 c.c.; and 4 : 6, 800 c.c.) gave a gum (0·5 g.) which was discarded since its infrared spectrum showed no hydroxyl band. Elution with light petroleum–benzene, benzene, and ether gave a series of gums (*ca.* 3 g.) which were combined and acetylated at 20° for 24 hr. to give a gum. This was adsorbed from light petroleum (60 c.c.) on alumina (350 g.). Elution with light petroleum (200 c.c.) and light petroleum–benzene (9 : 1, 400 c.c.) gave an oil (0·1 g.) which was discarded. Further elution with the solvents indicated gave the following fractions: (*a*) light petroleum–benzene (8 : 2, 200 c.c.) (70 mg., solid); (*b*) light petroleum–benzene (7 : 3, 700 c.c.) (1·2 g., gum); (*c*) light petroleum–benzene (6 : 4, 500 c.c.) (1 g., solid); (*d*) light petroleum–benzene (1 : 1, 400 c.c.; 4 : 6, 400 c.c.) (0·1 g.), and (*e*) benzene (200 c.c.) (90 mg., solid).

Fraction (*a*) gave plates (from methanol), m. p. 149—161°. Fraction (*b*) gave methyl 3α-acetoxylanosta-8 : 24-dien-21-oate as needles (50 mg.) (from aqueous acetone), m. p. and mixed m. p., 132—136°, $[\alpha]_D$ +9° (*c* 0·93). Light absorption: inflexions at 2430 and 2510 Å; ε 230 and 160. The mother liquors from these crystallisations yielded needles, m. p. 136—140·5° $[\alpha]_D$ +17° (*c* 0·18); no selective light absorption above 2200 Å.

Fraction (*c*) gave *methyl* 3α-*acetoxylanosta*-8 : 24-*dien*-21-*oate* as needles (from aqueous acetone), m. p. 135·5—137°, $[\alpha]_D$ +7° (*c* 1·5) (Found: C, 77·2; H, 10·15. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). Light absorption: Inflexions 2430 and 2510 Å; ε 125 and 85.

Fraction (*d*) gave needles (30 mg.), m. p. 142—144·5°, $[\alpha]_D$ +50·5° (*c* 0·68) (Found: C, 77·7; H, 10·05. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·3. $C_{35}H_{56}O_4$ requires C, 77·7; H, 10·45%); no selective light absorption above 2200 Å. Further chromatography of corresponding material indicated that it was a mixture of two closely related compounds. The first fraction from the chromatogram had m. p. 139—148°, $[\alpha]_D$ +54° (*c* 1·14), whilst the last fraction had m. p. 144—146·5°, $[\alpha]_D$ +54° (*c* 1·13).

From fraction (*e*) needles (from methanol), m. p. 141—160°, were obtained. Light absorption: Max., 2360 and 2430 Å; ε 7000 and 8000. Inflexion ε *ca.* 5000.

Examination of fraction (vi) from the initial chromatogram of the " light petroleum non-ketonic esters " will be detailed in a future publication.

Conversion of Methyl 3α-*Acetoxylanosta*-8 : 24-*dien*-21-*oate into Methyl* 3-*Oxolanosta*-8 : 24-*dien*-21-*oate* (*Methyl Pinicolate A*).—The acetoxy-ester (150 mg.) was treated with methanolic potassium hydroxide (15 c.c.; 10%) at 60° and then kept for 24 hr. at 20°. After dilution with water extraction with ether afforded a gum which was dissolved in acetone (20 c.c.) and oxidised with chromic acid solution (8N) according to the method of Bowers *et al.*[4] The product (98 mg.) was adsorbed from light petroleum–benzene (9 : 1; 10 c.c.) on alumina (10 g.). Elution with light petroleum–benzene (1 : 1; 100 c.c.) gave a solid (76 mg.) which yielded methyl 3-oxolanosta-8 : 24-dien-21-oate (methyl pinicolate A) (from aqueous acetone), m. p. and mixed m. p. 118—120°, $[\alpha]_D$ +70° (*c* 0·62). The infrared spectrum was identical with that of an authentic sample.

Preparation of Methyl 3β-*Acetoxylanosta*-7 : 9(11)-*dien*-21-*oate*.—Methyl 3β-acetoxylanost-8-en-21-oate [1] (220 mg.) was oxidised with perbenzoic acid (equiv. to 1·9 mol.) in benzene (10 c.c.) at 20° for 7 days. The mixture was then poured into sodium carbonate solution (5%).

Comparison of the Constants of Derivatives of the Japanese Acids and of Polyporenic Acid C and Tumulosic Acid.

	Japanese acid A series [2]		Polyporenic acid C series [4]	
Derivative	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
Free acid	260—263°	+ 8·6° (Py)	273—276°	+ 8° (Py)
Methyl ester	181—182·5°	+20·8°	198—199°	+10°
Monoacetate	177—180°	—	206—210°	—
	Japanese acid B series [2]		Tumulosic acid series [6]	
Derivative	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
Free acid	305—308°	+43°	306°	+ 8·1° (Py)
Methyl ester	178—178·5°	+44°	164—164·5°	+27°
Acetate	160—166°		214° (228°)	

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Extraction with ether afforded a gum which was treated in acetic acid (10 c.c.) with concentrated sulphuric acid (3 drops) at 100° for 5 min. and at 20° for 18 hr. The product (215 mg.), which contained an αβ-unsaturated ketone (band at 1665 cm.$^{-1}$), was adsorbed from light petroleum–benzene (2 : 1; 15 c.c.) on alumina (13 g.). Elution with light petroleum–benzene (3 : 2; 60 c.c.) afforded a solid (80 mg.) which gave *methyl* 3β-*acetoxylanosta*-7 : 9(11)-*dien*-21-*oate* as needles (from aqueous methanol), m. p. 146—148°, $[\alpha]_D$ +65° (*c* 0·8) (Found : C, 77·1; H, 10·2. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). Light absorption : Max. 2360, 2430, 2520 Å; ε 14,950, 17,500, and 11,700.

The authors thank Professor E. R. H. Jones, F.R.S., for his interest and advice, and Professor N. A. Sörensen, of the Institutt for Organisk Kjemi, Norges Tekniske Høgskole, Trondheim, for his generous help in collecting and supplying *Polyporus pinicola* Fr. One of them (J. B.) also thanks the United States Public Health Service for a Fellowship and another (H. F.) the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, MANCHESTER, 13.
THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February 15th,* 1957.]

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684. *Studies in the Synthesis of Terpenes. Part II.* The Preparation of an Intermediate for the Synthesis of Diterpenes.*

By J. D. COCKER and T. G. HALSALL.

The conversion of 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione (VI) into 5 : 5 : 9-trimethyl-$\Delta^{4(10)}$-octalin-1-ol (X) and thence by catalytic hydrogenation and oxidation into the corresponding decalone (XII) is described.

RECENTLY we isolated a new bicyclic diterpene, labdanolic acid (I),[1,2] from gum labdanum. A key step in the structure determination was the degradation of labdanolic acid to the C_{17} acid (II), previously obtained from marrubiin[3] and ambrein.[4] Little has been published on the synthesis of the acid (II) or of any diterpene of the manoöl–agathic acid group to which labdanolic acid belongs. Probably the most closely related compound so far synthesised is *rac*-ambreinolide (III) which has been prepared starting from dihydro-α-ionone.[4]

5 : 5 : 9-Trimethyl-*trans*-decal-1-one (XII) is a possible intermediate for the synthesis of acid (II), and of derivatives of the manoöl-agathic acid group of diterpenes and of deoxyonocerin (IV).[5] In this paper the synthesis of the decalone is described.

The diketone (VI) was the starting material. Previous methods [6-9] for its preparation do not give good yields; *e.g.*, that of Wendler, Slates, and Tishler [7] gives a 7% yield from 2-methyl*cyclo*hexane-1 : 3-dione and methyl vinyl ketone. Repetition of this procedure did not lead to a higher yield, but some 10-hydroxy-9-methyldecalin-1 : 6-dione (V) was also obtained. The diketone (VI) was made in the quantities needed by a method which will be described in the near future by Newman *et al.*[10] and by Robinson and his co-workers.[11]

* The paper, *J.*, 1956, 2431, is regarded as Part I.

[1] Cocker, Halsall, and Bowers, *J.*, 1956, 4259.
[2] Cocker and Halsall, *J.*, 1956, 4262.
[3] Burn and Rigby, *Chem. and Ind.*, 1955, 386.
[4] Wolff and Lederer, *Bull. Soc. chim. France*, 1955, 1466; cf. Dietrich and Lederer, *Helv. Chim. Acta*, 1952, **35**, 1148.
[5] Barton and Overton, *J.*, 1955, 2639.
[6] Wieland and Miescher, *Helv. Chim. Acta*, 1950, **33**, 2215.
[7] Wendler, Slates, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3816.
[8] Nazarov and Zav'yalov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 300. (Since our work was completed a better method for the preparation of the diketone (VI) has been described by Nazarov, Zav'yalov, Burmistrova, Gurvich, and Shmonina, *J. Gen. Chem.* (*U.S.S.R.*), 1956, 465.)
[9] Birch, Quartey, and Smith, *J.*, 1950, 1768.
[10] Newman, Stobaugh, and Swaminathan, forthcoming publication.
[11] Bannister, Jaeger, Robinson, Smith, and Sneeden, forthcoming publication.

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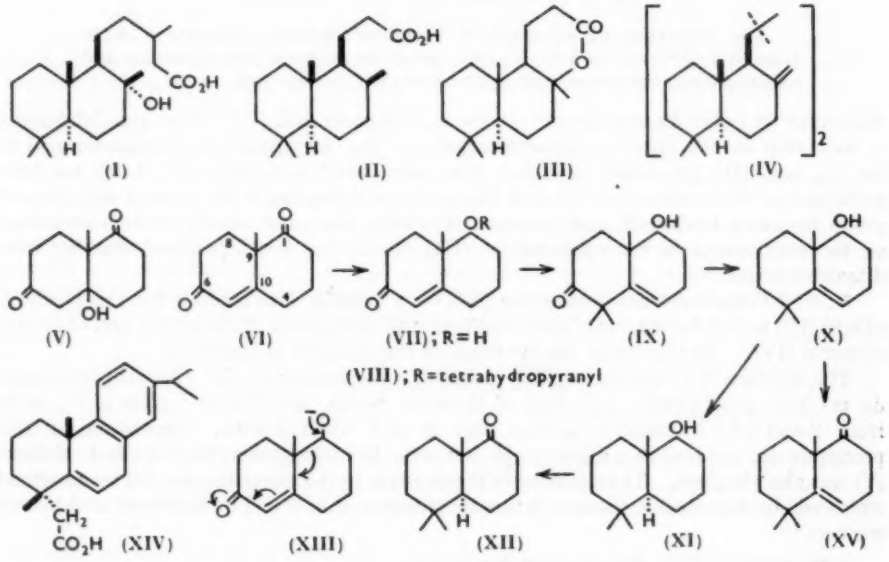
The diketone (VI) was reduced with recrystallised (*iso*propylamine) sodium borohydride; only the saturated keto-group was reduced[cf. 12] giving the oxo-alcohol (VII). The presence of an αβ-unsaturated ketone was shown by the ultraviolet maximum at 2385 Å. Use of non-recrystallised sodium borohydride gave poor results, presumably due to the presence of free alkali causing fission of the very alkali-labile diketone.[cf. 7] The oxo-alcohol had previously been prepared indirectly by Birch, Quartey, and Smith,[9] and also, in an optically active form, by microbiological reduction of the dione (VI).[13] The hydroxyl group is probably *cis* to the angular methyl group (*i.e.*, is equatorial), with attack by the borohydride ion from the side of the diketone opposite to that of the methyl group.[cf. 14]

The next step was the dimethylation of the α-carbon atom of the αβ-unsaturated ketone system. The methylation of such a system has been described by Woodward, Patchett, Barton, Ives, and Kelly.[15] Use of their method with the oxo-alcohol (VII) was not successful, owing to attack by the *tert.*-butoxide ion on the hydroxyl group and fission of the resulting anion (XIII). The tetrahydropyranyl ether (VIII) was, however, satisfactorily methylated; normally directly. It was obtained as prisms with a m. p. range of 6°, which may have been due to the presence of a small amount of a second stereoisomer of the ether involving the $C_{(2)}$-atom of the tetrahydropyran ring. Isolation of the methylation product involved loss of the ether grouping and the hydroxy-ketone (IX) was obtained



directly. Infrared and ultraviolet spectra showed the presence of a saturated keto-group, an isolated double bond, and a hydroxyl group, all consistent with structure (IX).

The hydroxy-ketone (IX) was reduced by the Wolff–Kishner method to the unsaturated alcohol (X), which could be hydrogenated in acetic acid, but not in ethanol, with a platinum catalyst. The resulting decalol (XI) showed no bands in the infrared region corresponding to a trisubstituted double bond. The decalol is assumed to be *trans*-fused since similar

[12] Norymberski and Woods, *Chem. and Ind.*, 1954, 518.
[13] Prelog and Acklin, *Helv. Chim. Acta*, 1956, **39**, 748.
[14] Courtney, Gascoigne, and Szumer, *J.*, 1956, 2119.
[15] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852.

reduction of 4 : 4-dimethylcholest-5-en-3-one followed by oxidation of the resulting dimethylcholestanol, gives 4 : 4-dimethylcholestan-3-one with rings A and B *trans*-fused.[16] Stork and Schulenberg [17] have obtained a similar result on hydrogenating the acid (XIV) with palladium–charcoal in acetic acid, (±)-homodehydroabietic acid being formed. Also, a model of the hydroxy-ketone (IX) indicates that the β-face is much more protected from attack than the α-face.

Oxidation of the decalol (XI) with chromic acid finally afforded the decalone (XII). Its infrared spectrum indicated a *gem*-dimethyl group. A band at 817 cm.$^{-1}$ (in carbon disulphide) was not due to a double bond. The decalone (XII) gave no colour with tetranitromethane whilst the octalone (XV) obtained by the oxidation of the unsaturated alcohol (X) did.

Since our preliminary account [18] Elad and Sondheimer [19] have also briefly described the preparation of the decalone (XII), and King, Ritchie, and Timmons [20] that of the benzoate of the closely related 6-hydroxy-5 : 5 : 9-trimethyldecal-1-one by a different route.

Experimental

M. p.s were determined on a Kofler block and are corrected. Ultraviolet light absorption data refer to ethanol solution. Light petroleum refers to the fraction with b. p. 60—80°.

Preparation of 9-Methyl-$\Delta^{5(10)}$*-octalin-1 : 6-dione* (VI) *by the Method of Wendler, Slates, and Tishler.*[7]—2-Methyl*cyclo*hexane-1 : 3-dione (10 g.) in methanol (155 c.c.), methyl vinyl ketone (11 c.c.), and triethylamine (1·5 c.c.) were kept at 12° for 17 hr. and shaken periodically. Removal of the solvent (reduced pressure) gave a pale yellow oil. The latter was dissolved in ether and washed with sodium hydrogen carbonate solution (5%), water, and saturated sodium chloride solution. Evaporation of the dried ether solution gave the Michael adduct (5·4 g.) as a yellow oil which was cyclised directly.

The adduct (5·4 g.) in benzene (20 c.c.) and a solution of aluminium *tert.*-butoxide (3·5 g.) in benzene (30 c.c.) were heated under reflux under nitrogen for 20 hr., then treated with ice and water, acidified (Congo red) with hydrochloric acid (3N), and extracted with ether to give a pale yellow oil. Light absorption : Max. 2440 Å; $E^{1\%}_{1\,cm.}$ 244. This oil was adsorbed from benzene on alumina (180 g.; neutralised and reactivated according to the method of Evans and Shoppee [21]). Elution with ether yielded 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione, prisms (0·20 g.), m. p. 49—50° (from light petroleum). Light absorption : Max. 2440 Å; $\varepsilon = 11{,}900$ (Wendler *et al.*[7] give m. p. 49—50°; light absorption : Max. 2440 Å; ε 12,000). Further elution with methanol afforded a solid, m. p. 176—182°, which crystallised slowly from ethyl acetate to give *10-hydroxy-9-methyldecalin-1 : 6-dione* (V) (0·30 g.) as needles, m. p. 184—185° (Found : C, 67·35; H, 8·25. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). Infrared absorption in "Nujol" suspension : bands at 3300 and 1700 cm.$^{-1}$.

The 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione used in the following experiments was prepared [10, 11] from diethylaminobutan-2-one and 2-methyl*cyclo*hexane-1 : 3-dione. The 2-methyl*cyclo*hexane-1 : 3-dione was prepared from resorcinol which was hydrogenated by Thompson's method [22] to *cyclo*hexane-1 : 3-dione; this was then methylated according to Stetter's method.[23] The 4-diethylaminobutan-2-one was prepared as described by Wilds and Shunk.[24]

5-Hydroxy-10-methyl-$\Delta^{1(9)}$*-octal-2-one* (VII).—9-Methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione (50 g.) in ethanol (1 l.) was treated at 8° with sodium borohydride (8·5 g.; recrystallised from *iso*propylamine) in ethanol (1 l.). The mixture was kept for 12 min. at 20° with occasional shaking and then treated with acetic acid (80 c.c.). Evaporation to dryness (reduced pressure), dissolution of the residue in water, and extraction of the solution with chloroform gave a gum, which was

[16] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.
[17] Stork and Schulenberg, *J. Amer. Chem. Soc.*, 1956, **78**, 250.
[18] Cocker and Halsall, *Chem. and Ind.*, 1956, 1275.
[19] Elad and Sondheimer, *Bull. Res. Council Israel*, 1956, **5**, *A*, 267.
[20] King, Ritchie, and Timmons, *Chem. and Ind.*, 1956, 1230.
[21] Evans and Shoppee, *J.*, 1953, 543.
[22] Thompson, *Org. Synth.*, 1947, **27**, 21.
[23] Stetter, *Chem. Ber.*, 1955, **88**, 77.
[24] Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469.

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dissolved in ether (75 c.c.), water (5 c.c.) was added and the solution was kept overnight at −5°. 5-Hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one monohydrate crystallised as prisms (35 g.), m. p. 47—56° (dependent upon the rate of heating) (Found: C, 66·85; H, 9·25. Calc. for $C_{11}H_{16}O_2,H_2O$: C, 66·65; H, 9·15%). Light absorption: Max. 2400 Å; ε 14,700. Infrared absorption in carbon tetrachloride: bands at 3630, 3400, 1670, and 1624 cm.$^{-1}$. Birch *et al.*[9] give m. p. 59—60°; $\lambda_{max.}$ 2400 Å; ε 14,700. When dried in a vacuum the crystals liquefied and the anhydrous substance could not be crystallised. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as prisms, m. p. 176—178° (Found: C, 56·55; H, 5·9; N, 15·5. $C_{17}H_{20}O_5N_4$ requires C, 56·65; H, 5·6; N, 15·55%). The *semicarbazone*, prepared by heating the hydroxy-ketone under reflux for 15 min. with aqueous–ethanolic semicarbazide hydrochloride and sodium acetate, crystallised from ethanol as prisms, m. p. 228—229° (Found: C, 60·9; H, 8·3; N, 17·8. $C_{12}H_{19}O_2N_3$ requires C, 60·75; H, 8·05; N, 17·7%).

10-*Methyl*-5-*tetrahydropyranyloxy*-$\Delta^{1(9)}$-*octal*-2-*one* (VIII).—5-Hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one (1·0 g.), dihydropyran (7 c.c.; redistilled from potassium hydroxide), and ether (2 c.c.) were treated with hydrochloric acid (2 drops). After the mixture had been kept for 2 days at 20° ether was added, and the ethereal solution was washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the ether under reduced pressure gave an oil (2·2 g.) which was adsorbed from light petroleum on neutral alumina (100 g.). Elution with light petroleum–benzene (4 : 1) gave an oil (0·76 g.), whose infrared spectrum did not show a carbonyl band. Further elution with light petroleum–benzene (1 : 1) yielded a fraction (0·7 g.) which gave 10-*methyl*-5-*tetrahydropyranyloxy*-$\Delta^{1(9)}$-*octal*-2-*one* as prisms (from light petroleum), m. p. 68—74° (Found: C, 72·7; H, 9·2. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·15%). Light absorption: Max.; 2385 Å; ε = 15,800. Infrared absorption in "Nujol" suspension: bands at 1670 and 1614 cm.$^{-1}$.

In later preparations the crude ether was not chromatographed but was methylated directly.

5-*Hydroxy*-1 : 1 : 10-*trimethyl*-Δ^8-*octal*-2-*one* (IX).—The tetrahydropyranyl ether (1·98 g.; 0·01 mole) in dry benzene (60 c.c.) was treated with potassium *tert.*-butoxide in *tert.*-butanol (1M) (50 c.c.; 0·05 mole) followed by methyl iodide (15 g.; 0·1 mole). The mixture was kept for 17 hr. at 20° and then water was added and the product was isolated with ether. The pale yellow oil, in methanol (50 c.c.), was treated with hydrochloric acid (3 drops) at 40° for 30 min. Dilution with water and extraction with ether gave a product (2·33 g.) which was adsorbed from benzene on neutral alumina (100 g.). Elution with benzene–ether (5 : 1) yielded a fraction which gave 5-*hydroxy*-1 : 1 : 10-*trimethyl*-Δ^8-*octal*-2-*one* (0·70 g.) as prisms, m. p. 92—94° (from light petroleum) (Found: C, 74·7; H, 9·5. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%). Infrared absorption in carbon disulphide: bands at 3580, 1709, 1645, 812, and 793 cm.$^{-1}$.

5 : 5 : 9-*Trimethyl*-$\Delta^{4(10)}$-*octalin*-1-*ol* (X).—5-Hydroxy-1 : 1 : 10-trimethyl-Δ^8-octal-2-one (9 g.), in redistilled diethylene glycol (480 c.c.), and hydrazine hydrate (40 c.c.; 100%) were heated at 90—100° for 1 hr. Potassium hydroxide (9 g.) was then added, the temperature raised to 215° (with distillation of water), and heating continued thereat for a further 6 hr. (If the temperature rose above 215°, the mixture became brown and the yield was lowered.) Dilution with water gave a solid (7·5 g.) which was purified by sublimation at 100°/10 mm. or crystallisation (aqueous methanol), giving 5 : 5 : 9-*trimethyl*-$\Delta^{4(10)}$-*octalin*-1-*ol* as needles, m. p. 122—122·5° (Found: C, 80·55; H, 11·45. $C_{13}H_{22}O$ requires C, 80·35; H, 11·4%). Light absorption: ε at 2060 Å = 2500; ε at 2100 Å = 1330; ε at 2140 Å = 520. Infrared absorption in carbon tetrachloride: bands at 3600, 1640, 1381, and 1363 cm.$^{-1}$.

5 : 5 : 9-*Trimethyl*-trans-*decalin*-1-*ol* (XI).—The octalinol (86 mg.) in acetic acid was hydrogenated in presence of Adams's platinum catalyst (100 mg.). Uptake of hydrogen ceased after 15 min. Removal of the catalyst, evaporation of the solvent under reduced pressure, and crystallisation of the solid from light petroleum at 0° gave 5 : 5 : 9-*trimethyl*-trans-*decalin*-1-*ol* as fine needles, m. p. 75—77° (Found: C, 79·65; H, 12·35. $C_{13}H_{24}O$ requires C, 79·55; H, 12·3%). Infrared absorption: band at 3600 cm.$^{-1}$.

5 : 5 : 9-*Trimethyl*-trans-*decal*-1-*one* (XII).—The decalinol (50 mg.) in acetone (5 c.c.) was oxidised with chromic acid (0·1 c.c.; 8N) according to the method of Bowers *et al.*[25] Dilution with water and extraction with ether afforded a solid which gave 5 : 5 : 9-*trimethyl*-trans-*decal*-1-*one* as thick rods (from aqueous methanol), m. p. 41—43° (Found: C, 80·5; H, 11·55. $C_{13}H_{22}O$ requires C, 80·35; H, 11·4%). The 2 : 4-*dinitrophenylhydrazone* formed prisms, m. p.

[25] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

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168·5—170°, from ethanol (Found : C, 61·6; H, 7·3; N, 15·1. $C_{19}H_{26}O_4N_4$ requires C, 60·95; H, 7·0; N, 14·95%).

5 : 5 : 9-*Trimethyl*-$\Delta^{4(10)}$-*octal*-1-*one* (XV).—5 : 5 : 9-Trimethyl-$\Delta^{4(10)}$-octalin-1-ol (0·105 g.) in acetone (5 c.c.) was treated with chromic acid (0·2 c.c.; 8N). Dilution with water and extraction with ether gave a non-crystallisable oil. 5 : 5 : 9-*Trimethyl*-$\Delta^{4(10)}$-*octal*-1-*one* 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as plates, m. p. 118—122° (Found : C, 61·15; H, 6·4. $C_{19}H_{24}O_4N_4$ requires C, 61·25; H, 6·5%).

The authors thank Professor E. R. H. Jones for his interest and Dr. Herchel Smith for advance details of the preparation of 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione. One of them (J. D. C.) thanks the Department of Scientific and Industrial Research for a maintenance grant. The infrared spectra were determined by Mr. F. Hastings under the supervision of Dr. F. B. Strauss.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, March 15th*, 1957.]

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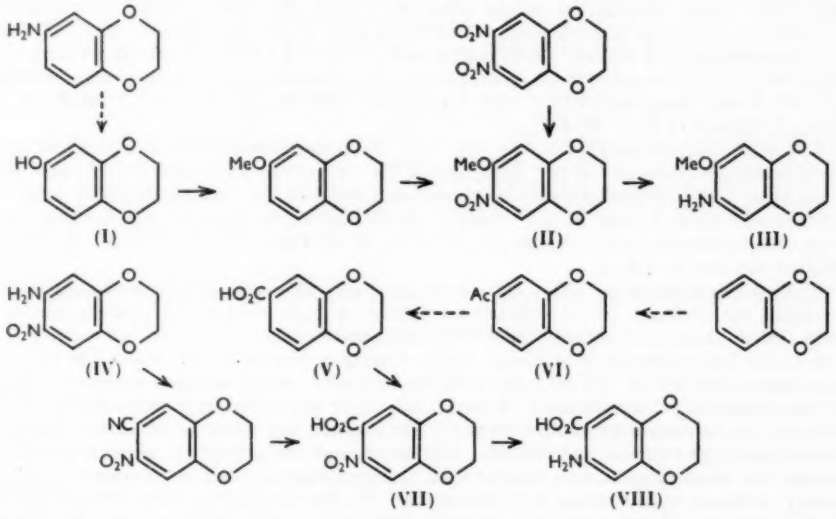
685. *Derivatives of Benzo-1 : 4-dioxan. Part IV.**

By P. M. HEERTJES, (MISS) B. J. KNAPE, H. C. A. VAN BEEK, and K. VAN DEN BOOGAART.

Preparation and orientation of some derivatives of 6-hydroxybenzo-1 : 4-dioxan and benzo-1 : 4-dioxan-6-carboxylic acid are reported.

THE reactions described in this paper are represented in the annexed chart; those marked with a broken arrow have been recorded elsewhere. The reactions have been carried out with conventional methods. The preparation of 6-hydroxybenzo-1 : 4-dioxan



(I) is given below in detail, since the published procedure [1] gave a different yield. For the preparation of 6-acetylbenzo-1 : 4-dioxan [2] (VI) and benzo-1 : 4-dioxan-6-carboxylic acid (V) [2] no experimental details have hitherto been given.

The structure of the mononitro-derivative (II) of 6-methoxybenzo-1 : 4-dioxan was

* Parts I—III, *J.*, 1954, 18, 1868; 1955, 1313.

[1] I. G. Farbenind. A.-G., B.P. 458,573/1936; J. R. Geigy, B.P. 566,732/1945.
[2] J. R. Geigy, U.S.P. 2,383,874/1945.

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established by the formation of this compound on treatment of 6 : 7-dinitrobenzo-1 : 4-dioxan with sodium methoxide in methanol. That of the mononitro-derivative (VII) of benzo-1 : 4-dioxan-6-carboxylic acid was proved by showing it to be identical with 7-nitrobenzo-1 : 4-dioxan-6-carboxylic acid obtained by converting 6-amino-7-nitrobenzo-1 : 4-dioxan (IV) into 6-cyano-7-nitrobenzo-1 : 4-dioxan, followed by hydrolysis of the cyano-group.

Nitration of benzo-1 : 4-dioxan-6-carboxylic acid gives 7-nitrobenzo-1 : 4-dioxan-6-carboxylic acid as the main product, although the reaction mixture also contains a second, unidentified mononitro-compound. 7-Nitrobenzo-1 : 4-dioxan-6-carboxylic acid can be decarboxylated partly, *e.g.*, when heated in glacial acetic acid; 6-nitrobenzo-1 : 4-dioxan was isolated from its crystallisation product; thus purification of crude 7-nitrobenzo-1 : 4-dioxan-6-carboxylic acid may present difficulties.

Experimental

M. p.s are corrected.

6-Hydroxybenzo-1 : 4-dioxan (I) (cf. Geigy [1]).—6-Aminobenzo-1 : 4-dioxan [3] (180 g.) was diazotised in N-sulphuric acid (1 l.) with sodium nitrite (51 g.) in water (250 ml.). The solution was then added during 2 hr. to a boiling mixture of sulphuric acid (400 ml.; *d* 1·84) and water (400 ml.). The thick red oil formed was decanted and distilled in a vacuum, giving crude *6-hydroxybenzo-1 : 4-dioxan* (108 g., 60%). The pure compound boiled at 170°/12 mm. (Found : C, 63·0; H, 5·4. Calc. for $C_8H_8O_3$: C, 63·1; H, 5·3%).

6-Methoxybenzo-1 : 4-dioxan.—6-Hydroxybenzo-1 : 4-dioxan (I) (30 g.), dissolved in 2N-potassium hydroxide (100 ml.), was shaken with dimethyl sulphate (27 g.), added in three equal portions during 15 min. The mixture was then refluxed for 30 min. and, after cooling, extracted with ether. After evaporation of the ether the *methyl ether* (30 g., 90%) was distilled in a vacuum (b. p. 110°/10 mm.) (Found : C, 64·9; H, 6·0. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%).

6-Acetoxybenzo-1 : 4-dioxan.—Refluxing 6-hydroxybenzo-1 : 4-dioxan (I) (12 g.) with acetic anhydride (10 g.) in benzene (25 ml.) containing a drop of concentrated sulphuric acid for 10 min. gave the *acetoxy-compound* (12·5 g., 80%), b. p. 150—152°/6 mm. (Found : C, 61·8; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%).

6-Methoxy-7-nitrobenzo-1 : 4-dioxan (II).—(*a*) To 6-methoxybenzo-1 : 4-dioxan (50 g.) in glacial acetic acid (500 ml.) at 25°, nitric acid (*d* 1·4; 25 ml.) in acetic acid (68 ml.) was added during 1½ hr. The precipitated *nitro-compound* was filtered off and washed with 50% acetic acid and then with alcohol (yield, 47 g.). Pouring the filtrate into water gave a further 10 g. (total, 90%). Crystallisation from alcohol raised the m. p. to 144·4—144·8° (Found : N, 6·6, 6·6. $C_9H_9O_5N$ requires N, 6·6%).

(*b*) 6 : 7-Dinitrobenzo-1 : 4-dioxan [4] was refluxed with an excess of 0·1N-methanolic sodium methoxide for 15 min. After repeated crystallisation from alcohol the product had m. p. 143·0—143·6° alone or mixed with the material obtained as in (*a*).

6-Amino-7-methoxybenzo-1 : 4-dioxan (III).—Cast-iron powder (8 g.), water (50 ml.), and hydrochloric acid (*d* 1·19; 0·8 ml.) were refluxed for 5 min. While nitrogen was passed through the flask 6-methoxy-7-nitrobenzo-1 : 4-dioxan (II) (7 g.) was added in portions during 30 min. Refluxing was continued for another 15 min. The mixture was cooled to 70°, made alkaline by sodium hydroxide solution, and filtered. The filtrate and the precipitate were extracted with benzene, the dried extracts were treated with hydrogen chloride, and the 6-amino-7-methoxybenzo-1 : 4-dioxan hydrochloride was filtered off. The free *base* (5·5 g., 90%) was obtained by treating the hydrochloride with aqueous alkali and had m. p. 63·8—64·5° (Found : N, 7·65, 7·7. $C_9H_{11}O_3N$ requires N, 7·7%).

The amine (2 g.) with acetic anhydride (2 ml.) in boiling benzene (10 ml.) gave the *acetyl* derivative (2 g.), m. p. 148·6—148·9° (from 1 : 1 aqueous alcohol) (Found : N, 6·2, 6·2. $C_{11}H_{13}O_4N$ requires N, 6·3%).

6-Acetylbenzo-1 : 4-dioxan [2] (VI).—To a stirred suspension of aluminium chloride (200 g.) in carbon disulphide (600 g.) at 10—15° a solution of acetyl chloride (118 g.) and benzo-1 : 4-dioxan

[3] Cf. Heertjes and Dahmen, *Rec. Trav. chim.*, 1943, **62**, 620.
Heertjes, Dahmen, and Wierda, *ibid.*, 1941, **60**, 569.

(194 g.) in carbon disulphide (450 g.) was added during 3½ hr. Thereafter the mixture was stirred at room temperature for 3 hr., refluxed for 3 hr., cooled, and poured on ice (2 kg.). The crude white acetyl compound was filtered off, washed with water, and crystallised once from 60% alcohol (yield, 224 g., 88%; m. p. 82—87°). Several crystallisations from dilute alcohol or acetone were necessary to obtain the pure compound, m. p. 86—87·5° (Found : C, 67·3; H, 5·6. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·6%).

Benzo-1 : 4-dioxan-6-carboxylic Acid [2] (V).—6-Acetylbenzo-1 : 4-dioxan (VI) (9 g.) was added in portions to a stirred 13% solution of sodium hypochlorite in water (110 ml.). The temperature was kept at 65°, first by the heat of reaction and later by external heat. After stirring of the mixture for 30 min. 25% sodium hydrogen sulphite solution (10 ml.) was added to remove excess of hypochlorite. The mixture was cooled to 25°, filtered, and acidified with hydrochloric acid. The white precipitate of benzo-1 : 4-dioxan-6-carboxylic acid was filtered off, washed with water, and crystallised once from 60% alcohol (yield, 8·5 g., 94%; m. p. 131·5—133°). Further purification was effected by continued crystallisation from dilute alcohol; the m. p. of the pure compound was 137—138° (Found : C, 59·7; H, 4·4. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·4%).

7-Nitrobenzo-1 : 4-dioxan-6-carboxylic Acid (VII).—(*a*) To a stirred solution of benzo-1 : 4-dioxan-6-carboxylic acid (20 g.) in glacial acetic acid (200 ml.) a mixture of nitric acid (*d* 1·52; 5 ml.) and sulphuric acid (*d* 1·84; 35 ml.) was added at room temperature during 30 min. After another 30 minutes' stirring the mixture was poured into water (300 ml.). The precipitated *7-nitro-acid* was filtered off, washed with acetic acid to remove benzo-1 : 4-dioxan-6-carboxylic acid, and crystallised once from dilute alcohol (yield, 17·5 g., 70%; m. p. 220°). The m. p. of the pure compound, obtained after several crystallisations, was 230—231° (Found : N, 6·2, 6·3. $C_9H_7O_6N$ requires N, 6·2%).

(*b*) 6-Amino-7-nitrobenzo-1 : 4-dioxan [5] was diazotised in 50% sulphuric acid, then added during 2 hr. to sodium cuprocyanide in boiling water. The resulting solution was filtered hot and on cooling deposited yellowish-white 6-cyano-7-nitrobenzo-1 : 4-dioxan. The crude cyanide was refluxed with 50% sulphuric acid for 10 hr., then diluted with an equal amount of water, and sodium nitrite solution was added slowly. The precipitate, when crystallised from dilute alcohol, had m. p. 226·5—227·5°, not depressed on admixture with the product obtained as above.

7-Aminobenzo-1 : 4-dioxan-6-carboxylic Acid (VIII).—7-Nitrobenzo-1 : 4-dioxan-6-carboxylic acid (2·7 g.) in 97·8% alcohol (50 ml.) was hydrogenated in presence of Raney nickel at 25°. The solution was filtered and the filtrate concentrated in a vacuum. The separated *7-aminobenzo-1 : 4-dioxan-6-carboxylic acid* was filtered off (1·6 g., 65%). Crystallised from dry methanol, it had m. p. 191—192° (Found : N, 7·2, 7·3. $C_9H_9O_4N$ requires N, 7·2%).

Acetylation as above gave the *acetamido-acid* (98%), m. p. 231—232° (from 60% alcohol) (Found : N, 5·9, 6·0. $C_{11}H_{11}O_5N$ requires N, 5·9%).

LABORATORY OF CHEMICAL TECHNOLOGY,
TECHNICAL UNIVERSITY, DELFT, HOLLAND.

[*Received, March 18th*, 1957.]

[5] Heertjes and Revallier, *Rec. Trav. chim.*, 1950, **69**, 262.

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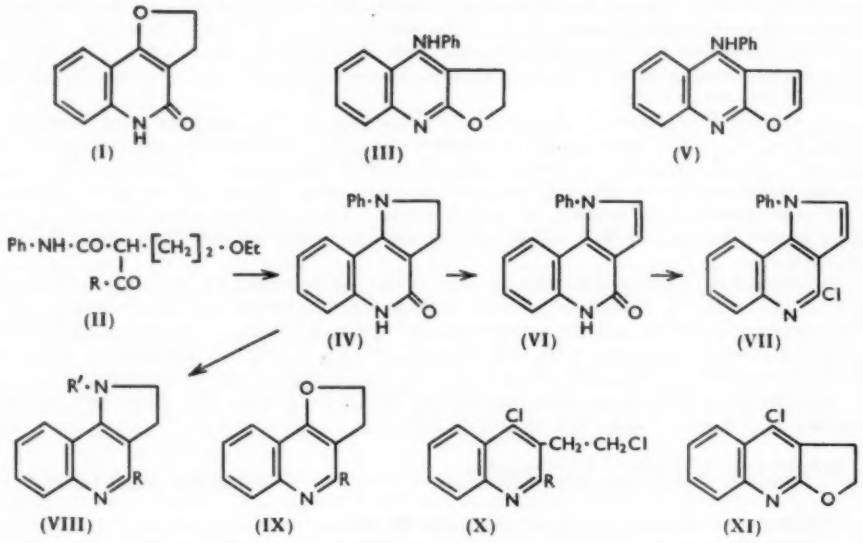
686. *The Preparation of a Pyrrolo(3′ : 2′-3 : 4)quinolone from (2-Ethoxyethyl)malondianilide.*

By M. F. Grundon and N. J. McCorkindale.

The structure of 1 : 2 : 4′ : 5′-tetrahydro-2-oxo-1′-phenylpyrrolo(3′ : 2′-3 : 4)quinoline (IV), prepared from (2-ethoxyethyl)malondianilide in refluxing diphenyl ether, was established by degradation to 4′ : 5′-dihydro-1′-phenylpyrrolo(3′ : 2′-3 : 4)quinoline (VIII; R = H, R′ = Ph) which was synthesised.

The intermediate in the preparation [1] of the dihydrofuranoquinolone (I) from aniline and ethyl (2-ethoxyethyl)malonate in boiling diphenyl ether is probably the monoanilide (II; R = OEt). When the dianilide (II; R = NHPh) was heated in diphenyl ether, a new product, $C_{17}H_{14}ON_2$, was obtained in good yield.

The compound can be formulated as the dihydrofuranoquinoline (III) or the pyrroloquinolone (IV), on the basis of its mode of formation and molecular formula. Dehydrogenation with palladium–charcoal gave the derivative, $C_{17}H_{12}ON_2$, (V) or (VI).



The intense infrared absorptions of the two new compounds at 1640—1650 cm.$^{-1}$ (NH·CO in a 2-quinolone [2]) favour the pyrroloquinolone structures (IV) and (VI), but the alternatives (III) and (V) are not excluded, as some anilino-derivatives absorb in the same infrared region.[3]

Reactions with phosphorus oxychloride confirmed the view that the compounds were quinolones. The dehydrogenation product gave the monochloroquinoline (VII), which showed no infrared absorption in the 1630—1700 cm.$^{-1}$ region. The compound, $C_{17}H_{14}ON_2$, afforded a dichloro-compound. This was not a derivative of the anilinoquinoline (III), formed by cleavage of the dihydrofuran ring, but a hydrochloride, from which the chloroquinoline (VIII; R = Cl, R′ = Ph) was obtained with alkali.

The dehydrogenation product was unaffected by hydrobromic acid in boiling acetic

[1] Grundon, McCorkindale, and (in part) Rodger, *J.*, 1955, 4284.
[2] Grundon and McCorkindale, *J.*, 1957, 2177.
[3] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1956, p. 219.

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acid, or by hydrochloric acid at 180°, in accord with the pyrroloquinolone structure (VI): 4-anilinoquinolines are hydrolysed by acid to 4-quinolones.[4] The compound, $C_{17}H_{14}ON_2$, on vigorous acid hydrolysis, gave the dihydrofuranoquinolone (I).

The proof of structure was completed by catalytic reduction of the chloro-compound (VIII; R = Cl, R′ = Ph) to 4′ : 5′-dihydro-1′-phenylpyrrolo(3′ : 2′-3 : 4)quinoline (VIII; R = H, R′ = Ph), which was synthesised.

Hörlein, Andersag, and Timmler [5] have prepared recently a series of dihydropyrroloquinolines [for example, (VIII; R = R′ = Me; and R = Me, R′ = CH_2Ph)] by heating the chloroquinoline (X; R = Me) with phenol and the appropriate amine. The chlorodihydrofurano(3′ : 2′-3 : 4)quinoline [2] (IX; R = Cl) furnished, with hydrogen and palladium–charcoal, the dihydrofuranoquinoline (IX; R = H), which was converted by phosphorus oxychloride into the dichloro-derivative (X; R = H). This, when heated with aniline and phenol, yielded the dihydropyrrolo(3′ : 2′-3 : 4)quinoline (VIII; R = H, R′ = Ph) identical with that prepared from the quinolone (IV).

In an attempt to synthesise the anilinoquinoline (III), the linear chlorodihydrofurano-(2′ : 3′-2 : 3)quinoline [2] (XI) was heated with phenol and aniline. The pyrroloquinolone (IV) was the only product isolated.

Experimental

(2-*Ethoxyethyl*)*malondianilide* (II; R = NHPh).—Nitrogen was passed slowly through a mixture of ethyl (2-ethoxyethyl)malonate (50 g.) and aniline (40·1 g.) at 180—190° (bath). After ethanol (2 mols.) had been evolved (4 hr.), the mixture was allowed to cool and solidify. Trituration with light petroleum (b. p. 40—60°) and then with ethanol, gave the *dianilide* (52·4 g., 75%), m. p. 153—154°, separating from ethanol in needles, m. p. 161—162° (Found: C, 69·4; H, 6·5; N, 8·8; OEt, 13·5. $C_{19}H_{22}O_3N_2$ requires C, 69·9; H, 6·8; N, 8·6; 1OEt, 13·8%).

1 : 2 : 4′ : 5′-*Tetrahydro*-2-*oxo*-1′-*phenylpyrrolo*(3′ : 2′-3 : 4)*quinoline* (IV).—(2-Ethoxyethyl)malondianilide (11·3 g.) was heated in diphenyl ether (50 c.c.) under reflux, the by-products (ethanol and water) being allowed to escape. After 5 hr., light petroleum (b. p. 40—60°) was added, giving a solid. By crystallisation from pyridine, the *dihydropyrroloquinolone* was obtained as pale brown prisms (5·14 g., 59%), m. p. 238—240°, raised to 246—247° by repeated recrystallisation from pyridine [$\lambda_{max.}$ 232 (ε 41,700), 268 (shoulder) (ε 9100), 331 mμ (ε 13,200)], $\nu_{max.}$ (in KBr) 1640(s) cm.$^{-1}$ (Found: C, 78·2; H, 5·6; N, 11·0. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%).

1 : 2-*Dihydro*-2-*oxo*-1′-*phenylpyrrolo*(3′ : 2′-3 : 4-)*quinoline* (VI).—1 : 2 : 4′ : 5′-Tetrahydro-2-oxo-1′-phenylpyrrolo(3′ : 2′-3 : 4)quinoline (0·5 g.) in diphenyl ether (15 c.c.) was heated under reflux with 10% palladium–charcoal (0·2 g.) for 15 hr., and the catalyst was removed by filtration. Addition of light petroleum precipitated the *pyrroloquinolone* (0·32 g., 64%), m. p. 249—250°, crystallising from ethanol in colourless prisms, m. p. 252—254°, $\lambda_{max.}$ 238 (ε 63,100), 274 (ε 7200) 284 (ε 6900), 315 (ε 9600), 328 mμ (ε 11,200), $\nu_{max.}$ (in KBr) 1650(s) cm.$^{-1}$ (Found: C, 78·2; H, 4·4; N, 10·8. $C_{17}H_{12}ON_2$ requires C, 78·4; H, 4·6; N, 10·8%).

2-*Chloro*-1′-*phenylpyrrolo*(3′ : 2′-3 : 4)*quinoline* (VII).—The foregoing pyrroloquinolone (0·5 g.) and phosphorus oxychloride (5 c.c.) were refluxed for 1 hr., and the excess of reagent was then removed under reduced pressure. The solid, obtained by the addition of water, crystallised from ethanol giving the *chloropyrroloquinoline* as colourless prisms (0·45 g., 84%), m. p. 143—144°, unchanged by recrystallisation from ethanol (Found: C, 73·3; H, 3·9; N, 10·7; Cl, 12·7. $C_{17}H_{11}N_2Cl$ requires C, 73·2; H, 4·0; N, 10·1; Cl, 12·7%).

2-*Chloro*-4′ : 5′-*dihydro*-1′-*phenylpyrrolo*(3′ : 2′-3 : 4)*quinoline* (VIII; R = Cl, R′ = Ph).—The dihydropyrroloquinolone (VI) (2 g.) and phosphorus oxychloride (13 c.c.) were refluxed for 1 hr., and the excess of reagent was removed. Addition of water gave the *hydrochloride* of the required base as a yellow solid (1·98 g., 81%), m. p. 180—186°, separating from ethanol in yellow prisms with unchanged m. p., $\nu_{max.}$ (in KBr) 2421(s) cm.$^{-1}$ (⩾NH^+) (Found: C, 64·6; H, 4·7; Cl, 22·7. $C_{17}H_{14}N_2Cl_2$ requires C, 64·4; H, 4·5; Cl, 22·4%).

A solution of the hydrochloride in chloroform was shaken with 0·5N-aqueous sodium hydroxide, dried, and evaporated, giving the *chloroquinoline*, m. p. 146—148°, quantitatively.

[4] von Braun and Heymons, *Ber.*, 1930, **63**, 3191; Backeberg, *J.*, 1931, 2814.
[5] Hörlein, Andersag, and Timmler, U.S.P. 2,691,023/1954 (*Chem. Abs.*, 1955, **49**, 14,813).

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The analytical sample crystallised from ethanol in colourless needles, m. p. 149—150°, $\nu_{max.}$ (in KCl) 1613(w), 1598(m), 1567(s), 1502(s) (Found: C, 73·0; H, 4·6; N, 10·6; Cl, 12·2. $C_{17}H_{13}N_2Cl$ requires C, 72·7; H, 4·7; N, 10·0; Cl, 12·6%).

Hydrolysis of 1 : 2 : 4′ : 5′-*Tetrahydro-2-oxo-1′-phenylpyrrolo*(3′ : 2′-3 : 4)*quinoline.*—The quinolone (1 g.) and hydrochloric acid (10 c.c.) were heated in a sealed tube at 150—160° for 1 hr., and the solution was diluted with water and extracted with chloroform. Concentration of the chloroform solution to small bulk gave a yellow solid (0·15 g.), m. p. 265—275°, crystallising from ethanol in pale yellow prisms, m. p. 276—278°, shown to be identical with 1 : 2 : 4′ : 5′ tetrahydro-2-oxofurano(3′ : 2′-3 : 4)quinoline [1] by a mixed m. p. determination and by infrared spectra.

4′ : 5′-*Dihydrofurano*(3′ : 2′-3 : 4-)*quinoline* (IX; R = H).—A solution of 2-chloro 4′ : 5′-dihydrofurano(3′ : 2′-3 : 4)quinoline [2] (2 g.) in ethanol (150 c.c.) containing potassium hydroxide (1·5 g.) was hydrogenated (1 mol. in 2½ hr.) at atmospheric pressure and room temperature with 10% palladium–charcoal (1 g.). The catalyst was removed, the solution evaporated, and the residue extracted with chloroform. The chloroform solution was shaken with several portions of aqueous acetic acid, and the combined acid solutions were made alkaline with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the chloroform afforded the *dihydrofuranoquinoline* as a yellow solid (1·65 g., 99%) separating from light petroleum (b. p. 40—60°) in colourless plates, m. p. 95—96° (Found: C, 77·1; H, 5·0; N, 8·0. $C_{11}H_9ON$ requires C, 77·2; H, 5·3; N, 8·2%).

4-*Chloro*-3-2′-*chloroethylquinoline* (X; R = H).—4′ : 5′-Dihydrofurano(3′ : 2′-3 : 4)quinoline (0·5 g.) and phosphorus oxychloride (5 c.c.) were refluxed for 2 hr., excess of oxychloride was removed under reduced pressure, and water was added. Chloroform extraction afforded the *chloroquinoline* (0·26 g., 40%), crystallising from light petroleum (b. p. 40—60°) in colourless rods, m. p. 75—76° (Found: C, 58·4; H, 3·9; N, 5·9. $C_{11}H_9NCl_2$ requires C, 58·4; H, 4·0; N, 6·2%).

After the above product had been removed, the aqueous solution was made alkaline with sodium hydroxide. Chloroform extraction gave a colourless solid (0·11 g.), m. p. 94—96°, alone or mixed with the starting material.

4′ : 5′-*Dihydro*-1′-*phenylpyrrolo*(3′ : 2′-3 : 4)*quinoline* (VIII; R = H, R′ = Ph).—(*a*) 2-Chloro-4′ : 5′-dihydro-1′-phenylpyrrolo(3′ : 2′-3 : 4)quinoline (0·157 g.), ethanol (15 c.c.), and 10% palladium–charcoal (0·1 g.) were hydrogenated at room temperature and atmospheric pressure until 1 mol. of hydrogen had been absorbed. The catalyst was removed and the solution evaporated. The residue in benzene–chloroform (1 : 1) was chromatographed on alumina. Elution with the same solvent, evaporation, and crystallisation from light petroleum (b. p. 60—80°) gave the *dihydropyrroloquinoline* in colourless needles (0·074 g., 54%), m. p. 109—112° (Found: C, 82·9; H, 5·8; N, 11·2. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%).

(*b*) A mixture of 4-chloro-3-2′-chloroethylquinoline (0·13 g.), phenol (0·12 g.), and aniline (0·22 g.) was heated at 170—180° (bath) for 3 hr., treated with 2N-aqueous sodium hydroxide, and extracted with chloroform. Evaporation of the chloroform solution furnished a dark-brown oil which was heated at 110° (bath)/0·1 mm. for 1 hr. to remove excess of aniline. A sublimate was obtained as a white solid (0·01 g.), m. p. 71—76°, undepressed by mixing with the starting material.

The residue was extracted with ether, and the ether solution was evaporated, giving a colourless solid (0·092 g.), m. p. 84—89°. Crystallisation from light petroleum (b. p. 40—60°) afforded the dihydropyrroloquinoline (0·076 g., 54%), m. p. 112—113°, undepressed by admixture with a sample prepared as in (*a*). The infrared spectra of the two samples were identical.

Reaction of 4-*Chloro*-4′ : 5′-*dihydrofurano*(2′ : 3′-2 : 3)*quinoline with Aniline.*—A mixture of the chlorofuranoquinoline [2] (1 g.), phenol (1 g.), and aniline (2 g.) was heated at 170—180° (bath) for 3 hr., and treated with 2N-aqueous sodium hydroxide. The precipitate was collected, and, after being washed with aqueous acetic acid and water, was obtained as a colourless solid (0·97 g.), m. p. 182—190°. Crystallisation from pyridine gave 1 : 2 : 4′ : 5′-tetrahydro-2-oxo-1′-phenylpyrrolo(3′ : 2′-3 : 4)quinoline as colourless prisms (0·615 g., 50%), m. p. 246—248°, not depressed on admixture with authentic material. The infrared spectra of the two samples were identical.

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UNIVERSITY OF GLASGOW.
THE QUEEN'S UNIVERSITY, BELFAST.

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687. *Dipole Moments and Molecular Structure. Part III.* Some Nitro-derivatives of Toluene.*

By R. C. Cass, H. Spedding, and H. D. Springall.

The dipole moments of 2 : 4-, 2 : 5-, 2 : 6-, and 3 : 5-dinitrotoluene and 2 : 4 : 6-trinitrotoluene have been measured and the results are used in a discussion of the mechanism of the "activation" of the methyl group in nitrotoluenes. Evidence is presented compatible with the steric suppression of $\overset{+}{\mathrm{Ar}}=\overset{+}{\mathrm{N}}\mathrm{O}_2^{3-}$ resonance in the 2- and 6-nitro-group in 2 : 6-dinitrotoluene and in 2 : 4 : 6-trinitrotoluene. No evidence has been found for hyperconjugation between the methyl group and the benzene nucleus.

The methyl groups in nitromethane, *p*-nitrotoluene, 2 : 4-dinitrotoluene, and 2 : 4 : 6-trinitrotoluene show many of the properties of active methylene groups: *e.g.*, they condense with benzaldehyde (nitromethane,[1] 2 : 4-dinitro-[2] and trinitro-toluene[3]), and undergo reactions of the Knovenagel–Mannich type with aldehydes and secondary bases (nitromethane,[4] 2 : 4-dinitrotoluene [5]). The effects with trinitrotoluene are in general slightly weaker than those with the other compounds. The methyl groups in 2 : 5-, 2 : 6-, and 3 : 5-dinitrotoluene are not "active."

In this investigation, aimed at the elucidation of the mechanism of the activation of methyl groups in nitrotoluenes, the atom polarisation terms for *p*-dinitrobenzene and *s*.-trinitrobenzene have been evaluated and the dipole moments of 2 : 4-, 2 : 5-, 2 : 6-, and 3 : 5-dinitrotoluene and of 2 : 4 : 6-trinitrotoluene in dilute solution have been determined.

Experimental

Preparation of Materials.—"AnalaR" benzene and dioxan (purified) were frozen four times, refluxed, respectively, over phosphoric oxide and with sodium, and distilled in a stream of dry air immediately before use.

p-Dinitrobenzene (from Hopkin and Williams), recrystallised from ethyl alcohol, had m. p. 173° (Starkey [6] gives m. p. 173°).

2 : 4-Dinitrotoluene (from B.D.H.), recrystallised from acetone, had m. p. 69·0—70° (Garner and Abernethy [7] give m. p. 70·5°).

The 2 : 5-isomer (from Hopkin and Williams), recrystallised from benzene, had m. p. 51—52° (lit.,[7] m. p. 51·2°).

The 2 : 6-isomer (from Kahlbaum), recrystallised from acetone, had m. p. 64·5—65·5° (lit.,[7] m. p. 64·3°).

The 3 : 5-isomer was prepared from *p*-acetamidotoluene by the method of Cohen and McCandlish,[8] and recrystallised from ethyl alcohol; it had m. p. 93° (Cohen and McCandlish [8] give m. p. 92—93°).

2 : 4 : 6-Trinitrotoluene,[9] recrystallised from acetone, had m. p. 81° (Garner and Abernethy [7] give m. p. 81·1°).

s.-Trinitrobenzene, prepared from trinitrotoluene by oxidation and decarboxylation (Clark and Hartman [10]) and recrystallised from acetic acid, had m. p. 122° (lit.,[10] m. p. 121—122°).

Determination of Dipole Moments.—These were made in solution at 25° by the refractivity method, the heterodyne technique being used for measurement of the dielectric constant, as

* Part II, *J.*, 1957, 188.

[1] Worrall, *Org. Synth.*, Coll. Vol. I, 1948, p. 413.
[2] Thiele and Escale, *Ber.*, 1901, **34**, 2842.
[3] Pfeiffer and Monath, *Ber.*, 1906, **39**, 1306.
[4] Hope and Robinson, *J.*, 1910, **97**, 2114.
[5] McLeod and Robinson, *J.*, 1921, **110**, 1470.
[6] Starkey, *Org. Synth.*, Coll. Vol. II, 1943, p. 225.
[7] Garner and Abernethy, *Proc. Roy. Soc.*, 1921, *A*, **99**, 213.
[8] Cohen and McCandlish, *J.*, 1905, **87**, 1271.
[9] Stettbacher, "Schiess- und Sprengstoffe," Barth, Leipzig, 1933, p. 261.
[10] Clark and Hartman, *Org. Synth.*, Coll. Vol. I, 1948, p. 541.

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described in Parts I [11] and II.[12] Parallel determinations in benzene and in dioxan solution were made on all the substances to minimise the risk of not detecting solvent–solute interactions between benzene and the nitro-compounds. The agreement between the dipole results obtained with the two solvents showed that nothing anomalous was happening in the benzene solutions, and the benzene values are used in the theoretical discussions, because the non-polar benzene is, from the point of view of dielectric-constant studies, the more satisfactory solvent.

The results are given in Table 1 (e = dielectric constant).

TABLE 1.

w	e	v	n	w	e	v	n
p-*Dinitrobenzene* (M, 168·108) : *in benzene*				*in* 1 : 4-*dioxan*			
0·015720	2·2865	1·13481	1·50270	0·012998	2·226	0·96674	1·4236
0·020080	2·2875	1·13225	1·50285	0·016181	2·228	0·96572	1·42385
0·026182	2·2905	1·12979	1·50330	0·024811	2·234	0·96348	1·4252
0·029326	2·2925	1·12803	1·50340	0·037980	2·2425	0·95988	1·4268
s.-*Trinitrobenzene* (M, 213·108) : *in benzene*				*in* 1 : 4-*dioxan*			
0·025615	2·287	1·1313	1·5039	0·017010	2·234	0·9675	1·4249
0·039391	2·292	1·1243	1·5046	0·032925	2·243	0·9612	1·4270
0·057245	2·299	1·1139	1·5059	0·036907	2·245	0·9603	1·4270
0·058267	2·300	1·1138	1·5057				
2 : 4-*Dinitrotoluene* (M, 182·122) : *in benzene*				*in* 1 : 4-*dioxan*			
0·020229	2·504	1·1364	1·5040	0·010975	2·368	0·9707	1·4241
0·032259	2·641	1·1311	1·5045	0·019742	2·480	0·9682	1·4251
0·048703	2·832	1·1240	1·5053	0·038493	2·746	0·9640	1·4275
0·061784	2·987	1·1183	1·5059	0·058187	3·014	0·9585	1·4299
2 : 5-*Dinitrotoluene* (M, 182·134) : *in benzene*				*in* 1 : 4-*dioxan*			
0·0071692	2·280	1·1389	1·50235	0·021480	2·238	0·96479	1·42453
0·014012	2·286	1·1358	1·5027	0·031209	2·2465	0·92642	1·42692
0·021211	2·291	1·1332	1·5030	0·038625	2·253	0·96071	1·42687
0·021940	2·292	1·1318	1·5030	0·057011	2·269	0·95566	1·42934
0·030508	2·299	1·1290	1·5034				
2 : 6-*Dinitrotoluene* (M, 182·122) : *in benzene*				*in* 1 : 4-*dioxan*			
0·022776	2·383	1·1356	1·5035	0·021190	2·340	0·9680	1·4255
0·032460	2·432	1·1314	1·5039	0·040131	2·435	0·9590	1·4275
0·047751	2·513	1·1249	1·5045	0·060030	2·579	0·9584	1·4296
0·051291	2·530	1·1232	1·5047				
3 : 5-*Dinitrotoluene* (M, 182·134) : *in benzene*				*in* 1 : 4-*dioxan*			
0·007920	2·364	1·13880	1·5022	0·029211	2·558	0·96302	1·4259
0·01084	2·394	1·13766	1·5024	0·035314	2·670	0·96126	1·42636
0·02083	2·511	1·13317	1·5028	0·052210	2·883	0·95693	1·42886
0·02930	2·610	1·12932	1·5032	0·057901	2·964	0·95557	1·4296
				0·061075	3·000	0·95492	1·42997
2 : 4 : 6-*Trinitrotoluene* (M, 227·124) : *in benzene*				*in* 1 : 4-*dioxan*			
0·029045	2·306	1·1312	1·5033	0·022650	2·269	0·9674	1·4246
0·045990	2·323	1·1232	1·5041	0·031543	2·277	0·9644	1·4258
0·064720	2·344	1·1138	1·5051	0·035166	2·280	0·9633	1·4261
0·082530	2·362	1·1046	1·5063	0·047543	2·297	0·9591	1·4281

The derived data on the extrapolations of e, v, and n to $w = 0$ and the corresponding slopes α, β, and γ are given in Table 2, together with the molar total and electronic polarisation terms. These are evaluated from the slopes α, β, and γ, by using the expressions: [12]

$$_{T}P_{2} = M(0{\cdot}34110 + 0{\cdot}18818\alpha + 0{\cdot}29787\beta) \text{ for benzene solutions}$$
$$= M(0{\cdot}28124 + 0{\cdot}16388\alpha + 0{\cdot}28910\beta) \text{ for dioxan solutions}$$

and

$$_{E}P_{2} = M(0{\cdot}33797 + 0{\cdot}29513\beta + 0{\cdot}56986\gamma) \text{ for benzene solutions}$$
$$= M(0{\cdot}24782 + 0{\cdot}25475\beta + 0{\cdot}51263\gamma) \text{ for dioxan solutions}$$

Aromatic polynitro-compounds show rather high atom polarisation ($_{A}P_{2}$) terms.[13] The polarisations at radio frequency and at visible frequency of p-dinitrobenzene were measured

[11] Springall, Hampson, May, and Spedding, *J.*, 1949, 1524.
[12] Mortimer, Spedding, and Springall, *J.*, 1957, 188.
[13] Sutton, *Ann. Reports*, 1940, **37**, 63; *Discuss. Faraday Soc.*, 1946, 170.

in both benzene and dioxan; the average difference (12·3 c.c.) for this non-polar substance was taken as that part of the atom polarisation, ${}_{A}P'_{2}$, neglected in visible-frequency measurements, and this value used for the " neglected " atom polarisation term for dinitrotoluenes. (This procedure is likely to be quite valid for 2 : 5-dinitrotoluene, where the nitro-groups are *para* to one another; but may give a slight overestimate of the ${}_{A}P'_{2}$ terms for the 2 : 4-, 2 : 6-, and 3 : 5-isomer, where the nitro-groups are *meta* to one another. The derived values of the dipole moments of the last compounds are therefore lower limit values. The possible error so introduced is, however, too small to affect the general conclusions.)

Similar measurements were made on *s.*-trinitrobenzene and the correspondingly derived " neglected " atom polarisation term of 10·9 c.c. was used with trinitrotoluene.

TABLE 2.

No.	Compound	Solvent	ε_1'	α	v_1'
1	*p*-Dinitrobenzene	Benzene	2·277	0·572	1·1423
		Dioxan	2·218	0·690	0·9704
2	2 : 4-Dinitrotoluene	Benzene	2·277	11·624	1·1452
		Dioxan	2·214	13·763	0·9734
3	2 : 5-Dinitrotoluene	Benzene	2·276	0·768	1·1426
		Dioxan	2·220	0·870	0·9703
4	2 : 6-Dinitrotoluene	Benzene	2·274	5·178	1·1454
		Dioxan	2·210	6·154	0·9732
5	3 : 5-Dinitrotoluene	Benzene	2·268	11·660	1·1429
		Dioxan	2·202	13·186	0·9705
6	*s.*-Trinitrobenzene	Benzene	2·277	0·392	1·1455
		Dioxan	2·225	0·556	0·9737
7	2 : 4 : 6-Trinitrotoluene	Benzene	2·275	1·055	1·1459
		Dioxan	2·232	1·133	0·9749

No.	β	n_1'	γ	${}_{T}P_{2}$	${}_{E}P_{2}$	${}_{A}P'_{2}$	μ
1	−0·437	1·5018	0·0562	53·55	40·59	12·96	0
	−0·272	1·4217	0·1314	53·08	41·34	11·74	0
2	−0·435	1·5029	0·050	437·8	43·3	12·3	4·33
	−0·254	1·4228	0·122	448·6	44·7	12·3	4·38
3	−0·428	1·5020	0·0470	63·24	43·42	12·3	0·58
	−0·254	1·4217	0·133	64·71	45·77	12·3	0·57
4	−0·432	1·5026	0·040	216·5	42·5	12·3	2·81
	−0·246	1·4230	0·114	221·9	43·4	12·3	2·85
5	−0·435	1·5019	0·0450	438·16	42·84	12·3	4·33
	−0·257	1·4219	0·133	442·17	45·63	12·3	4·33
6	−0·546	1·5025	0·060	54·8	44·9	9·9	0
	−0·370	1·4229	0·120	56·6	44·8	11·9	0
7	−0·498	1·5018	0·0525	88·9	50·2	10·9	1·16 *
	−0·331	1·4217	0·130	84·3	53·0	10·9	1·0 †

* μ for trinitrotoluene in benzene was measured by Le Fèvre and Le Fèvre (*J.*, 1950, 1829) with the results: ${}_{T}P_{2} = 87·2$; ${}_{E}P_{2} = 48·7$; ${}_{T}P_{2} - {}_{E}P_{2} = 38·5$. Our ${}_{T}P_{2} - {}_{E}P_{2}$ (= 38·7) is almost identical with Le Fèvre and Le Fèvre's value, but where we allow the extra 11 c.c. for the ${}_{A}P'_{2}$ term (yielding a moment = 1·16 D) Le Fèvre and Le Fèvre proceed directly from ${}_{T}P_{2} - {}_{E}P_{2}$ to the evaluation of the dipole moment and so obtain the value 1·37 D.

† The moment of trinitrotoluene was determined in carbon tetrachloride solution also, and μ = 1·26 D obtained as the result, indicating absence of unexpected solvent effect. Owing, however, to the extremely low solubility in the solvent the result is not of high accuracy and the experimental details are not tabulated.

The dipole moments are evaluated by the Debye expression

$$\mu_{25} = 0{\cdot}2211\sqrt{({}_{T}P_{2} - {}_{E}P_{2} - {}_{A}P'_{2})}\ \text{D}$$

As a further check on the behaviour of trinitrotoluene in benzene solution, the non-existence of a chemical compound between solute and solvent was shown by a freezing-point diagram of the trinitrotoluene–benzene system, which (Fig. 1) shows the typical " single discontinuity–no maximum " form expected for a two-component, single-liquid phase system without compound formation.

Discussion

The dipole moments of the simpler mononitroalkanes $R{\cdot}NO_2$ in solution are as follows: R = Me,[14] 3·1 D; Et,[15] 3·2 D; Bu^t, 3·3 D.[16] The general agreement among these results

[14] Weissberger and Sängewald, *Ber.*, 1932, **65**, 701.
[15] Hunter and Partington, *J.*, 1933, 309.
[16] Sutton, *Trans. Faraday Soc.*, 1934, **30**, 789.

indicates that there are no mesomeric interaction moments of the hyperconjugation type $\overset{H+}{C}H{=}\overset{+}{N}O_2^{2-}$ operating with R = Me or Et. This is also shown by the fact that the C–N bond length in nitromethane has the value 1·47 ± 0·02 Å [17,18] characteristic of a C–N single bond.[19] The slight variation in the moments is probably due to induction effects and we take the value for Bu^t–NO_2 (3·3 D) as being the true C_{alk}–NO_2 moment in solution.

In nitrobenzene, however, the extra resonance effect due to contribution from ionic structures of the type $\overset{+}{A}r = \overset{+}{N}O_2^{2-}$ causes an increase in the moment to 3·94 D,[16,20] and tends to constrain the Ar·NO_2 system to a planar configuration because of C=N double bonding. If, in this system, the nitro-group is forced by bulky *ortho*-substituents to rotate about the C–N bond, the oxygen atoms leaving the plane of the benzene ring, the extra resonance is impaired and the corresponding $\mu(C{-}NO_2)$ is reduced from $\mu(C_{ar}{-}NO_2)$ towards $\mu(C_{alk}{-}NO_2)$. This effect has been investigated (i) in nitrodurene and allied compounds by dipole moments,[21] (ii) in nitromesitylene by dipole moments [22] and Raman spectra,[23] and (iii) in 4-dimethylamino-2-methyl-1-nitrobenzene and in 5-dimethylamino-1 : 3-dimethyl-2-nitrobenzene by ultraviolet absorption spectra.[24]

FIG. 1.

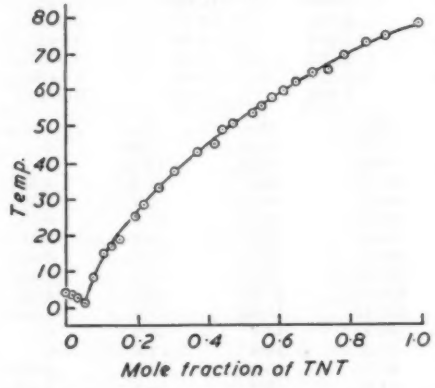
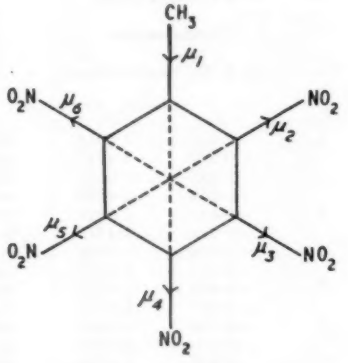
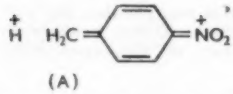


FIG. 2.



The results indicate strong steric suppression of the $\overset{+}{A}r{=}\overset{+}{N}O_2^{2-}$ resonance when both positions next to the nitro-group have methyl substituents but only weak steric effects with only one *ortho*-substituent.

In view of the above findings, we may expect with the nitrotoluenes, (*a*) no mesomeric interaction moments of type (A) and (*b*) some steric suppression of the $\overset{+}{A}r{=}\overset{+}{N}O_2^{2-}$ resonance with nitro-groups adjacent to the methyl group. The suppression is likely to be weak when only one of the *ortho*-positions is substituted by a nitro-group but strong when both are so substituted.



(A)

(a) *Mononitrotoluenes.* The dipole moments of *o*-, *m*-, and *p*-mononitrotoluene [25] are susceptible to a simple approximate vector analysis if absence of mesomeric interaction moments is assumed and induction effects are neglected. In Table 3 are listed (i) the

[17] Brockway, *Rev. Mod. Phys.*, 1936, **8**, 231.
[18] Rogowski, *Ber.*, 1942, **75**, 244.
[19] Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1941, p. 167.
[20] Williams, *Phys. Z.*, 1928, **29**, 174; see also Jenkins, *J.*, 1934, 480.
[21] Birtles and Hampson, *J.*, 1937, 10.
[22] Hammick, New, and Williams, *J.*, 1934, 30.
[23] Saunders, Murray, and Cleveland, *J. Amer. Chem. Soc.*, 1941, **63**, 3121.
[24] Remington, *ibid.*, 1945, **67**, 1841.
[25] Williams, *Phys. Z.*, 1928, **29**, 683.

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values of the resultant moments $\bar{\mu}$ calculated on the simple regular hexagon molecular model (Fig. 2) with the assumption that $\mu_1 = 0{\cdot}41$ (the toluene moment [26]) and (*a*) $\overset{+}{\text{Ar}}=\overset{+}{\text{N}}\text{O}_2^{2-}$ resonance operating [$\mu(\text{C}-\text{NO}_2) = 3{\cdot}94$ D] and (*b*) this resonance suppressed [$\mu(\text{C}-\text{NO}_2) = 3{\cdot}30$ D)], and (ii) the observed resultant moments.

TABLE 3.

	$\bar{\mu}_{calc.}$ *a*	$\bar{\mu}_{calc.}$ *b*	$\bar{\mu}_{obs.}$		$\bar{\mu}_{calc.}$ *a*	$\bar{\mu}_{calc.}$ *b*	$\bar{\mu}_{obs.}$
	Mononitrotoluenes				*Dinitrotoluenes*		
o-	3·75	3·14	3·75	2 : 4-	4·16	3·92	4·33
m-	4·16	3·53	4·20	2 : 5-	0·41	0·93	0·58
p-	4·35	3·71	4·50	2 : 6-	3·53	2·89	2·81
	2 : 4 : 6-*Trinitrotoluene*			3 : 5-	4·35	4·35	4·33
	0·41	1·05	1·16				

The agreement between $\bar{\mu}_{calc.}$ (*a*) and $\bar{\mu}_{obs.}$ is in accordance with the expectations suggested by the general theory.

The dipole moments of 2 : 4-, 2 : 5-, 2 : 6-, and 3 : 5-dinitrotoluene and of trinitrotoluene were subjected to a similar analysis.

(b) *Dinitrotoluenes.* The results with the mononitrotoluenes encouraged the use of vector models with $\mu_1 = 0{\cdot}41$ D and $\mu_3 = \mu_4 = \mu_5 = 3{\cdot}94$ D. Alternative models were investigated dependent on the setting of μ_2 and μ_6, either (*a*) 3·94 D or (*b*) 3·30 D.

In the results (Table 3) the moderately good agreement between $\bar{\mu}_{calc.}$ (*a*) and $\bar{\mu}_{obs.}$ for 2 : 4- and 2 : 5-dinitrotoluene, and the good agreement between $\bar{\mu}_{calc.}$ (*b*) and $\bar{\mu}_{obs.}$ for the 2 : 6-compound again are in accordance with the expectations. The calculated resultant moment of the 3 : 5-compound is unaffected by (*a*) or (*b*) hypotheses as to μ_2 and μ_6; agreement with observation here too is good.

[Hardung [27] has reported, without experimental details, the measurement of the dipole moments of all six dinitrotoluenes in benzene solution. His results for the 2 : 4-, 2 : 5-, 2 : 6-, and 3 : 5-isomer are respectively 3·75, 0·94, 2·95, and 4·05 D. His aim was to correlate the reactivity of the methyl group with the difference between the calculated and the observed moments. He attributed any such difference to a change in the moment of the CH_3–C grouping, and stated that the correlation was, on the whole, as expected. The most striking discrepancy was with the 2 : 4-isomer (Hardung's experimental result for this compound differs markedly from ours) but the 2 : 5-isomer yields an anomalous result also.]

(c) 2 : 4 : 6-*Trinitrotoluene.* In view of the results with the mono- and dinitrotoluenes, two vector models only were considered : (*a*) using $\mu_1 = 0{\cdot}41$, $\mu_2 = \mu_4 = \mu_6 = 3{\cdot}94$ D; (*b*) using $\mu_1 = 0{\cdot}41$, $\mu_2 = \mu_6 = 3{\cdot}30$, and $\mu_4 = 3{\cdot}94$ D; model (*b*) is the more likely. The results are given in Table 3. The agreement between $\bar{\mu}_{calc.}$ (*b*) and $\bar{\mu}_{obs.}$ again is in accordance with expectations.

The results are compatible with the effects on $\overset{+}{\text{Ar}}=\overset{+}{\text{N}}\text{O}_2^{2-}$ resonance summarised in Table 4.

TABLE 4. $\overset{+}{\text{Ar}}=\overset{+}{\text{N}}\text{O}_2^{2-}$ *resonance effects* (+ = *operative*; S = *suppressed*).

Posn. of NO_2	MNT	2 : 4-DNT	2 : 5-DNT	2 : 6-DNT	3 : 5-DNT	TNT
2-	+	+	+	S		S
3-	+				+	
4-	+	+				+
5-	+		+		+	
6-	+			S		S

This analysis lends support to the views: (i) that hyperconjugated ionic structures, involving the methyl group, are unlikely to contribute significantly to the resting structures

[26] Tiganik, *Z. phys. Chem.*, 1931, **13**, *B*, 425.
[27] Hardung, *Helv. Phys. Acta*, 1947, **20**, 1470; 1948, **21**, 445.

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of the nitrotoluenes, the difference between the moments of toluene and trinitrotoluene being attributable to the steric lowering of the 2- and 6-NO_2 moments rather than to any mesomeric increase in the CH_3–C moment; (ii) that it is possible to correlate activity of the methyl group in nitrotoluenes with the extent to which excited $\overset{+}{A}r=\overset{+}{N}O_2^{2-}$ structures having the nuclear cationic charge located on the methyl-bearing $C_{(1)}$ atom, contribute to the molecule.* The activity is potentially strong in compounds in which the nitro-groups are in the 2-, 4-, or 6-position but is weakened by the steric suppression of $\overset{+}{A}r=\overset{+}{N}O_2^{2-}$ structures in the 2 : 6-dinitrotoluene system. Direct steric shielding of the methyl group by 2- and 6-nitro-groups probably assists in the depression of activity.

We are indebted to Drs. G. S. Davy and D. C. C. Smith for assistance with some of the work on the trinitrobenzene–benzene diagram, to Mr. B. C. Jones for polarisation measurements on *p*-dinitrobenzene and on 2 : 5- and 3 : 5-dinitrotoluene, and to Albright and Wilson Limited for a grant.

THE UNIVERSITY, MANCHESTER.
UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE,
KEELE, STAFFORDSHIRE. [*Received, January 28th*, 1957.]

* It may be noted that the very reactive methyl group in nitromethane is directly bonded to a cationic " ammonium " nitrogen atom.

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688. *Dipole Moments and Molecular Structure. Part IV.* Ether Derivatives of Pentaerythritol.*

By I. T. MILLAR, C. T. MORTIMER, and H. D. SPRINGALL.

The dipole moments of pentaerythritol tetramethyl ether and of 5 : 5′-*spiro*bis-1 : 3-dioxan have been measured, and the results are used in a consideration of possible limitations of rotation about the $C_{(1)}$–$C_{(2)}$ and $C_{(2)}$–O bonds in pentaerythritol derivatives.

IN the work described in Part II,[1] concerned primarily with the structure of pentaerythritol tetranitrate, dipole-moment evidence was presented for (i) the inhibition of free rotation about the $C_{(1)}$–$C_{(2)}$ bond in each " leg " (A) of the pentaerythritol molecule [dipole moments of compounds (I; X = I, Br, or Cl) are zero], and (ii) freedom of rotation about the $C_{(2)}$–O bond [dipole moments of derivatives (II), where Y is such that the O–Y moment acts along the O–Y bond, are finite, ~2 D].

The aim of this work has been to investigate these points further by a study of the dipole moments of pentaerythritol tetramethyl ether (II; Y = Me) and of 5 : 5′-*spiro*bis-1 : 3-dioxan (III).

EXPERIMENTAL

Preparation of Materials.—" AnalaR " benzene was frozen four times and refluxed over phosphoric acid. It was distilled immediately before use.

Pentaerythritol tetramethyl ether was prepared as described by Backer and Dijken.[2] 5 : 5′-*spiro*Bis-1 : 3-dioxan was prepared by Read's method.[3]

Determinations of Dipole Moment.—These were made in benzene solutions at 25° by the refractivity method, the heterodyne technique being used for the measurement of dielectric constant, as in Parts I [4] and II.[1]

* Part III, preceding paper.

[1] Mortimer, Spedding, and Springall, *J.*, 1957, 188.
[2] Backer and Dijken, *Rec. Trav. chim.*, 1936, **55**, 22.
[3] Read, *J.*, 1912, **101**, 2093.
[4] Springall, Hampson, May, and Spedding, *J.*, 1949, 1524.

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The derived data on the extrapolations of e, v, and n (Table 1) to $w = 0$ and the corresponding slopes α, β, and γ are given in Table 2, together with the molar total ($_TP_2$) and electronic ($_EP_2$) polarisation terms. These are evaluated from α, β, and γ by the expressions : [1]

$$_TP_2 = M(0{\cdot}34110 + 0{\cdot}18818\alpha + 0{\cdot}29787\beta)$$
$$_EP_2 = M(0{\cdot}33797 + 0{\cdot}29513\beta + 0{\cdot}56986\gamma)$$

The dipole moments are calculated from the total and electronic polarisation terms (the small undetermined part of the atom polarisation being neglected) by the Debye expression $\mu_{75} = 0{\cdot}2211\sqrt{(_TP_2 - _EP_2)}$ D.

TABLE 1.

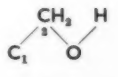
w	v	e	n	w	v	e	n
Pentaerythritol tetramethyl ether (M, 192·250)				5 : 5′-*spiro*Bis-1 : 3-dioxan (M, 160·166)			
0·01804	1·1394	2·3072	1·50260	0·01593	1·1406	2·3466	1·50283
0·03029	1·1348	2·3325	1·50221	0·02664	1·1364	2·3972	1·50260
0·04337	1·1296	2·3557	1·50190	0·03571	1·1331	2·4415	1·50242
0·05334	1·1263	2·3771	1·50151	0·04452	1·1297	2·4778	1·50217

TABLE 2. *Data for* (*A*) *pentaerythritol tetramethyl ether and* (*B*) 5 : 5′-spiro*bis*-1 : 3-*dioxan, extrapolated to* $w = 0$.

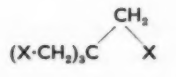
	e_1'	α	v_2'	β	n_1'	γ	$_TP_2$	$_EP_2$	μ
A ...	2·2730	1·95	1·1459	−0·372	1·50312	−0·0289	114·7 ± 1·4	40·7 ± 0·5	1·91 ± 0·01
B ...	2·2727	4·73	1·1463	−0·376	1·50316	−0·0224	17·8 ± 1·6	18·3 ± 0·3	0

DISCUSSION

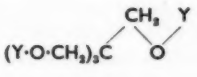
Previously only two compounds of type (II) have been subjected to dipole-moment studies, pentaerythritol [5] itself, Y = H ($\mu \sim 2$ D), and the tetranitrate,[1] Y = NO_2 (μ = 2·48 D).* Of these, pentaerythritol is insufficiently soluble in suitable solvents to permit its dipole moment to be studied in solution (the accepted value for μ comes from early molecular-beam studies), while the tetranitrate is sufficiently soluble in dioxan, alone, of the range of suitable solvents, for accurate experimental dipole measurement. These solubility restrictions made very desirable the study of a genuine type (II) compound soluble in a non-polar solvent. The tetramethyl ether is such a substance and the observed moment of 1·91 D in benzene solution gives useful support to the earlier findings.



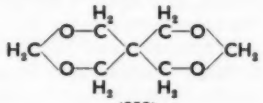
(A)



(I)



(II)



(III)

We interpret this observed moment as solely due to the out-of-phase rotation of the four O–CH_3 systems about the $C_{(2)}$–O bonds. If this interpretation is correct, then the restriction of this rotation to be achieved by replacing the four methyl groups by two methylene bridges to give 5 : 5′-*spiro*bis-1 : 3-dioxan (III) should result in a reduction of the dipole moment. [The individual bond moments are unlikely to differ widely in (II; Y = Me and in (III)).] The observed zero moment for the *spiro*-compound supports this view, indicating that the methylene bridges have inhibited $C_{(2)}$–O rotation to such an extent that the compound is stable in a highly symmetrical configuration in which the four O–CH_2 bond moments have a zero resultant.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE,
KEELE, STAFFORDSHIRE.

[*Received, January 28th*, 1957.]

* The moment of the tetra-acetate (II; Y = Ac) has been measured [6] (μ = 2·2 D), but in this compound the moment of the O–Y system does *not* act along the O–Y bond, so that the compound would show a resultant moment, due to out-of-phase free rotation about the four O–Y bonds, irrespective of freedom or inhibition of rotation about the $C_{(2)}$–O bonds.

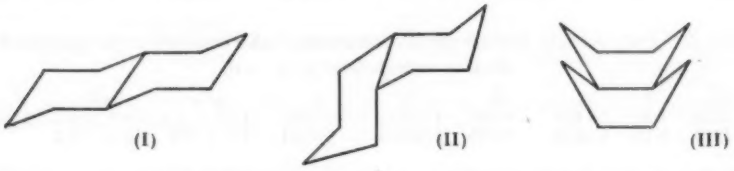
[5] Estermann, *Z. phys. Chem.*, 1929, **2**, *B*, 287; Estermann and Wohlwill, *ibid.*, 1933, **20**, *B*, 195.
[6] Othner and Freyss, *Annalen*, 1930, **484**, 131.

689. *Molecular Polarisability. The Molar Kerr Constants and Conformations of* cis- *and* trans-*Decalins.*

By (Mrs.) C. G. Le Fèvre and R. J. W. Le Fèvre.

The longitudinal and transverse polarisabilities of the carbon–carbon and carbon–hydrogen bonds, as deduced previously,[1] have been used to calculate *a priori* the molar Kerr constants of *trans*-decalin and of the two alternative structures for its *cis*-isomer. The values obtained, when compared with the results of direct measurement, favour " two-chair " conformations for both decalins.

The belief that *trans*- and *cis*-decalin are[2] (I) and (II) rather[3] than (I) and (III) respectively appears to be based on electron-diffraction studies[2,4] and calculations of energy differences;[5] only the former can be recognised as giving direct evidence. We



(I) (II) (III)

have therefore examined the Kerr effects of the two isomers and determined for each its molar Kerr constant. The results are compared with those computed for the three different geometrical arrangements by use of the known [1] polarisabilities of carbon–carbon and carbon–hydrogen bonds by the procedure previously described.[1]

Experimental

cis- *and* trans-*Decalin.*—Decalin (" redistilled " grade from British Drug Houses Ltd.) was fractionated;[6] the samples obtained finally had the following properties: *trans*-isomer, b. p. 68°/10 mm., d_4^{15} 0·8742, d_4^{20} 0·8702, n_D^{20} 1·4699; *cis*-isomer, b. p. 74°/10 mm., d_4^{15} 0·8981, d_4^{20} 0·8938, n_D^{20} 1·4809; these constants are in reasonable agreement with values in the literature.[7–9] The *trans*-form greatly predominated in the initial decalin.

Apparatus and Technique.—Electric double refractions were determined in solutions in carbon tetrachloride as described in refs. 1, 10, and 11, wherein are defined the various symbols used. A useful improvement in the closure of the cells has been to remove the brass ferrules (Fig. 2 of ref. 10) and to seal in their places standard B24 sockets. The smaller-diameter ends of the related cones were then ground and polarimeter cover glasses attached with Araldite type 101. Strains associated with the swelling of the rubber washers used previously are thereby avoided and two end-cones can be used with a number of cell bodies containing plates of different lengths and separations. Dielectric constants were measured in the circuit recently noted.[12] Tables 1 and 2 set out the observations and results.

[1] Le Fèvre and Le Fèvre, *J.*, 1956, 3549; *Rev. Pure Appl. Chem.*, 1955, **5**, 261.
[2] Bastiansen and Hassel, *Tids. Kjemi*, 1943, **3**, 91; 1946, **6**, 870; *Nature*, 1946, **157**, 765.
[3] Cf. *Ann. Reports*, 1924, **21**, 93; 1935, **32**, 307; Hückel, *Annalen*, 1925, **441**, 1; *Ber.*, 1925, **58**, 1449; and many standard text books.
[4] Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149.
[5] Barton, *J.*, 1948, 340; 1953, 1027; Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 2118; cf. Klyne, " Progress in Stereochemistry," Butterworths, London, 1954, Ch. 2.
[6] Seyer and Walker, *J. Amer. Chem. Soc.*, 1938, **50**, 2125.
[7] Beilstein's " Handbuch," V, 92, V* 46, V** 56; Selected Values of Properties of Hydrocarbons, Table 29*a* (Part 1), Amer. Petroleum Inst. Project 44, Carnegie Inst. of Tech., Pittsburgh, 1950.
[8] Seyer and Barrow, *J. Amer. Chem. Soc.*, 1948, **70**, 802.
[9] Mizuhara and Seyer, *ibid.*, 1953, **75**, 3274.
[10] Le Fèvre and Le Fèvre, *J.*, 1953, 4041.
[11] *Idem, ibid.*, 1954, 1577.
[12] Buckingham, Chau, Freeman, Le Fèvre, Rao, and Tardif, *J.*, 1956, 1405.

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TABLE 1. *Observations on solutions in carbon tetrachloride.*

10^6w_2	ε^{30}	d_4^{30}	n_D^{25}	ΔB_D^{25}
0	2·2176	1·57480	1·4575	—
		cis-*Decalin*		
4493	2·2174	1·56948	—	*ca.* 0
6962	2·2172	1·56642	—	−0·001
14,080	2·2167	1·55798	1·4578	$-0·001_5$
40,020	—	—	—	$-0·003_5$
43,045	2·2149	1·52521	1·4591	$-0·003_5$
				trans-*Decalin*
14,577	2·2157	1·55543	—	0·001
34,396	2·2127	1·53218	1·4582	0·002
38,805	2·2124	1·52684	—	0·002
52,470	—	—	—	$0·002_5$
83,778	2·2068	1·47471	1·4588	0·004

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = -0·061_2$
$\Delta d = -1·225w_2 + 1·7w_2^2$
$\Sigma\Delta n/\Sigma w_2 = 0·033_3$
$\Delta B = -0·115w_2 + 0·7w_2^2$

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = -0·133$
$\Delta d = -1·284w_2 + 1·1w_2^2$
$\Sigma\Delta n/\Sigma w_2 = 0·016_9$
$\Delta B = 0·058_3w_2 - 0·14w_2^2$

TABLE 2. *Calculation of* ${}_\infty P_2$ *and* ${}_\infty({}_mK_2)$.

	$\alpha\varepsilon_1$	β	${}_\infty P_2$ (c.c.)	γ	δ	${}_\infty({}_mK_2) \times 10^{12}$
cis-Decalin	−0·061	−0·778	44·1	0·023	$-1·6_4$	0·15
trans- ,, ...	−0·133	−0·815	44·0	0·012	$0·83_6$	$2·8_0$

DISCUSSION

Dielectric Polarisations.—According to the M.I.T. Tables [13] *cis*-decalin has been examined in both benzene and carbon tetrachloride, but the *trans*-isomer in benzene only. The reference to Puchalik [14] is not available in Australia and the abstracts [14] merely state that $\mu = 0$ without quoting the polarisations actually found. The entry for Seyer and Barrow [15] is incorrect in that their data are for the pure liquids, not for solutions in benzene, and a value by Fairbrother [16] is omitted. Present and past measurements are compared in Table 3. The dielectric constants and densities as functions of temperature, given in refs. 15—18, correspond to a slight increase of total polarisation with rise of temperature (*e.g.*, 0·4 c.c. from 25° to 142° according to Sutton *et al.*[18]; *ca.* 1 c.c. for the separate isomers between 20° and 100° according to Seyer and Barrow [15]); these facts, together with the very small dielectric loss noted for decalin by Whiffen [19] (cf. Heston and Smyth [20]), clearly indicate the non-polarity of both decalins.

TABLE 3. *Total polarisations (c.c.) recorded for the decalins.*

Author(s)	Temp.	Unseparated mixture	*cis*-isomer	*trans*-isomer	Ref.
Lautsch	20°	42·3	—	—	17
Sutton, New, and Bentley ...	25°	43·7	—	—	18
Fairbrother	20°	43·8	43·7	44·3	16
Seyer and Barrow	20°	—	44·4	44·9	15
Present work *	30°	—	44·1	44·0	

All observations were on pure liquids over temperature ranges throughout which P did not diminish, except for that marked *, which is for solution in carbon tetrachloride.

Molar Kerr Constants.—As shown in Table 1, the addition of *cis*-decalin lowers, while that of *trans*-decalin raises, the Kerr constant of carbon tetrachloride. The values obtained for ${}_\infty({}_mK_2) \times 10^{12}$, namely 0·15 and 2·8, indicate that the *cis*-isomer is more isotropically polarisable than is the *trans*.

[13] Wesson, "Tables of Electric Dipole Moments," Technology Press, Massachusetts Institute of Technology, 1948.
[14] Puchalik, *Acta Phys. Polon.*, 1933, **2**, 305; cf. *Brit. Abs.*, 1936, 408; *Chem. Zentr.*, 1935, **1**, 3914.
[15] Seyer and Barrow, *J. Amer. Chem. Soc.*, 1948, **70**, 802.
[16] Fairbrother, *Proc. Roy. Soc.*, 1933, *A*, **142**, 173.
[17] Lautsch, *Z. phys. Chem.*, 1928, **1**, *B*, 118.
[18] Sutton, New, and Bentley, *J.*, 1933, 652.
[19] Whiffen, *Trans. Faraday Soc.*, 1950, **46**, 124.
[20] Heston and Smyth, *J. Amer. Chem. Soc.*, 1950, **72**, 99.

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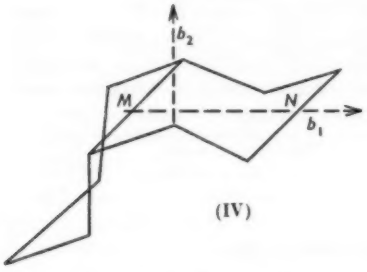
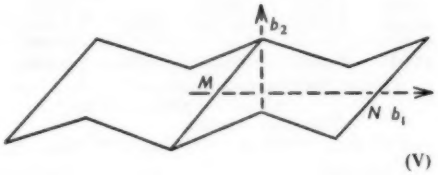
The birefringences are small and not far from the limits set by the apparatus. The molar Kerr constant was also determined of a liquid sample obtained by cutting B.D.H. " redistilled " decalin from 185—190° (this fraction formed the greater part of the initial



(IV)



(V)

material; both from its physical constants and the weakness of its infrared absorption [21] at *ca.* 11·4 μ it appeared to be largely *trans*-decalin). B_D^{20} was $0{\cdot}103_5 \times 10^{-7}$ which, with $d_4^{20} = 0{\cdot}8722$, $\varepsilon_{20} = 2{\cdot}166$, and $n_D^{20} = 1{\cdot}4714$, corresponds to ${}_mK_{\text{liquid}} = 2{\cdot}8_3 \times 10^{-12}$; agreement with the ${}_\infty({}_mK_2)$ measured in carbon tetrachloride is good.

Prediction of Molar Kerr Constants for Conformations (I), (II), *or* (III).—The polarisability semi-axes expected for the two decalins can be calculated by use of the information given in ref. 1 for *cyclo*hexane and the C–C and the C–H bond. Let the b's for the isomers be disposed as indicated in (IV) and (V). Writing $b_1^{cyH} = b_2^{cyH}$ and b_3^{cyH} for the appropriate polarisabilities of *cyclo*hexane, b^{CH} for the semi-axis of the (isotropic) C–H link, and respectively b_L^{CC} and b_T^{CC} for the longitudinal and transverse polarisabilities of the C–C bond, and assuming all intercarbon angles to be tetrahedral, we have

(i) for *cis*-decalin :

$$b_1 = b_1^{cyH} + 3b_T^{CC} + 2b_L^{CC}\cos^2 19°\,28'\cos^2 30° + 2b_T^{CC}\sin^2 30° + 2b_T^{CC}\sin^2 19°\,28'\cos^2 30° + 6b^{CH}$$

$$b_2 = b_1^{cyH} + 2b_T^{CC} + b_L^{CC}\cos^2 19°\,28'(1 + 2\cos^2 60) + b_T^{CC}\sin^2 19°\,28'(1 + 2\cos^2 60°) + 2b_T^{CC}\sin^2 60° + 6b^{CH}$$

$$b_3 = b_3^{cyH} + 2b_L^{CC} + 3b_L^{CC}\sin^2 19°\,28' + 3b_T^{CC}\cos^2 19°\,28' + 6b^{CH}$$

(ii) for *trans*-decalin :

$$b_1 = 2b_1^{cyH} - b_T^{CC} - 6b^{CH}$$

$$b_2 = 2b_1^{cyH} - b_L^{CC}\cos^2 19°\,28' - b_T^{CC}\sin^2 19°\,28' - 6b^{CH}$$

$$b_3 = 2b_3^{cyH} - b_L^{CC}\sin^2 19°\,28' - b_T^{CC}\cos^2 19°\,28' - 6b^{CH}$$

Insertion of the values [1] (all in units of 10^{-23} c.c.) $b_1^{cyH} = 1{\cdot}117$, $b_3^{cyH} = 0{\cdot}975$, $b_L^{CC} = 0{\cdot}0986$, $b_T^{CC} = 0{\cdot}0274$, and $b^{CH} = 0{\cdot}0635$, gives

	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$
For *cis*-decalin	$1{\cdot}73_0$	$1{\cdot}73_0$	$1{\cdot}65_9$
,, *trans*- ,, ...	$1{\cdot}82_6$	$1{\cdot}76_2$	$1{\cdot}53_4$

These correspond to molar Kerr constants of $0{\cdot}25 \times 10^{-12}$ and $3{\cdot}5 \times 10^{-12}$, respectively. Considering the various assumptions made (geometry of the decalins, that ${}_DP/{}_EP = 1{\cdot}1$, etc.) and the difficulty of measuring a small ${}_\infty({}_mK_2)$ with accuracy, we regard the agreement between prediction and experiment as satisfactory, and as strengthening our earlier conclusions regarding the anisotropic polarisability of the aliphatic C–C single bond.[1]

Finally it is of interest to mention that application of similar calculations to the (now generally discarded) 2-boat structure (III) leads to $10^{23}b_1 = 1{\cdot}824$, $10^{23}b_2 = 1{\cdot}721$, and $10^{23}b_3 = 1{\cdot}571$, whence ${}_mK$ should be $2{\cdot}43 \times 10^{-12}$. This is definitely higher than the

[21] Seidman, *Analyt. Chem.*, 1951, **23**, 559.

$0{\cdot}15 \times 10^{-12}$ observed, and thus further contradicts (III) as the correct formula for *cis*-decalin; the argument seems quantitatively not inferior to that [5] drawn from empirical or semi-empirical energy differences.

The authors thank Messrs. H. H. G. McKern and R. O. Hellyer of the Museum of Applied Arts and Sciences, Sydney, for fractionating the decalin.

SCHOOL OF CHEMISTRY, UNIVERSITY OF SYDNEY,
N.S.W., AUSTRALIA.

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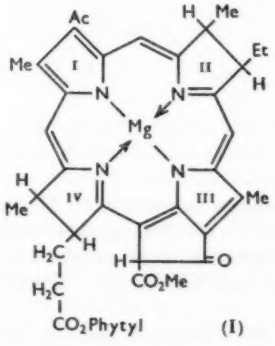
690. *Some Novel Hydroporphyrins.*

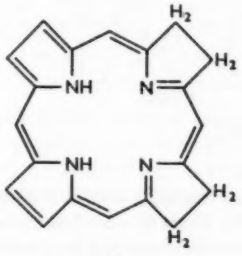
By ULLI EISNER.

The two isomeric octaethyltetrahydroporphins have been prepared by the reduction of octaethylporphin with sodium and *iso*pentyl alcohol. Reduction of the corresponding chlorin afforded, in addition to the tetrahydro-derivatives, the octaethylhexa- and an octaethylocta-hydroporphin. Light-absorption properties are discussed, and quantitative stepwise dehydrogenation of the hydro-pigments has been studied.

COMPARATIVELY little is known about porphyrins at a higher hydrogenation level than the dihydro-derivatives or chlorins. Bacteriochlorophyll (I), the naturally occurring dihydrochlorophyll derivative, is the only compound which has been extensively studied. Its constitution was elucidated by Fischer [1] and by Mittenzwei [2] and its formulation as a tetrahydroporphin is now generally accepted. The position of the two pairs of " extra " hydrogen atoms has never been established unequivocally. Fischer [1] assigned them to the pyrrole nuclei II and IV. Seely,[3] however, suggested that the alternative I–IV or III–IV structures were not excluded by the chemical evidence. Recent molecular-orbital calculations [4] have shown that the two isomeric tetrahydroporphyrins, the " adjacent "



(I)



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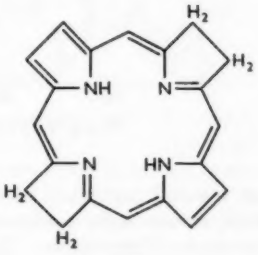


(III)

(II) and " opposite " (III) types,* would differ considerably in their light-absorption properties. The long-wave bands of (II) and (III) have been predicted to lie below and above that of the corresponding chlorin respectively. These calculations place Fischer's structure of bacteriochlorophyll on a sound basis.

Even less is known about synthetic hydroporphyrins. Dorough and Miller [5] obtained

* Throughout this work the " adjacent " and " opposite " types will be referred to as *a*- and *b*-tetrahydroporphyrins respectively.

[1] Fischer–Orth, " Die Chemie des Pyrrols," Springer Verlag, Leipzig, 1940, II/2, p. 305.
[2] Mittenzwei, *Z. physiol. Chem.*, 1942, **275**, 93.
[3] Seely, U.S. Atomic Energy Comm., U.C.R.L. 2417, 1953.
[4] Barnard and Jackman, *J.*, 1956, 1172.
[5] Dorough and Miller, *J. Amer. Chem. Soc.*, 1952, **74**, 6106.

two compounds, "α" and "β," in very low yield by the catalytic hydrogenation of *meso*tetraphenylchlorin. Compound "α" was tentatively formulated as a tetrahydroporphyrin. The sole evidence was the similarity of its spectrum to that of bacteriochlorophyll and its photo-oxidation to the chlorin with 1 : 2-naphthaquinone. No structure was proposed for the "β" compound although photo-oxidation to the chlorin with 1 : 2-naphthaquinone was observed. Seely *et al.*[3, 6] reduced zinc *meso*tetraphenylporphin photochemically with benzoin and obtained, apart from some of the corresponding zinc chlorin, a new compound to which they assigned a tetrahydro-structure on the basis of its dehydrogenation to the zinc porphin or chlorin. It was subsequently shown to be identical with Dorough and Miller's "β" compound. Under certain conditions a second pigment was obtained which could be converted into the tetrahydro-compound and was therefore formulated as a hexahydro-derivative.

The reduction, by sodium and higher alcohols, of the iron complex of ætioporphyrin was first examined by Fischer *et al.*[7] who claimed to have obtained the corresponding chlorin

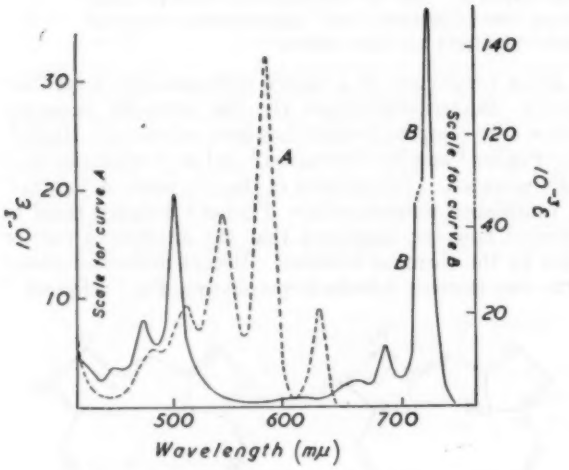


FIG. 1. *A*, a-*Octaethyltetrahydroporphin*. *B*, b-*Octaethyltetrahydroporphin*.

and a red "perhydro"-derivative which could readily be converted into the chlorin. These results were confirmed by Corwin and his co-workers[8] who isolated the pure "perhydro"-derivative. This was formulated as a tetrahydroætioporphyrin on the basis of its quantitative dehydrogenation to ætiochlorin by potassium molybdicyanide. Neither analytical nor light absorption data were recorded.

It was decided to re-investigate the above reduction and to establish, if possible, the nature of the products, starting from the readily available octaethylporphin.[9] Reduction of the iron complex with sodium in boiling *iso*pentyl alcohol (cf. ref. 9) afforded a complex mixture of pigments which were separated by chromatography on magnesium oxide. The bands, in order of elution, were: a yellow band containing traces of *b*-octaethyltetrahydroporphin (IV); a pink band of *a*-octaethyltetrahydroporphin (V); a green band of octaethylchlorin (VI); and a red band of unchanged starting material. Traces of three other pigments were also observed: a red and a green pigment (both unidentified) whose light

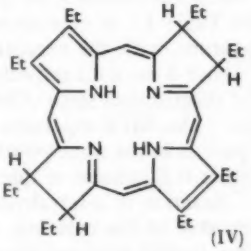
[6] Seely and Calvin, *J. Chem. Phys.*, 1955, **23**, 1068.
[7] Fischer, Platz, Helberger, and Niemer, *Annalen*, 1930, **479**, 49.
[8] Schlesinger, Corwin, and Sargent, *J. Amer. Chem. Soc.*, 1950, **72**, 2867.
[9] Eisner, Lichtarowicz, and Linstead, *J.*, 1957, 733.

absorptions were very similar to those of the *a*-tetrahydroporphin (V) and the chlorin (VI) respectively; and a purple material which is discussed below.

a-*Octaethyltetrahydroporphin.*—This pigment (V), together with the chlorin (VI) which was formed in about 30% yield, constituted the bulk of the product. It was extremely soluble in all organic solvents and crystallised only with difficulty and considerable loss. Its solutions are magenta with an intense characteristic orange fluorescence. They are stable in the absence of light. It has a typical four-banded spectrum of porphyrin type and a Soret band (see Table 1 and Fig. 1). Fischer and Helberger [10] recorded light-absorption maxima at 583 and 543 mμ for the " perhydro "-derivative of a porphinmonocarboxylic acid, in good agreement with the spectral properties of our material. Its spectrum is also in good agreement with the predicted light-absorption [4] of a tetrahydroporphin in which the two pairs of " extra " hydrogen atoms are placed on adjacent pyrrole nuclei, and with Dorough and Miller's " β " compound.

This pigment (V) forms a blue solution in the presence of mineral acids. It is not stable under these conditions but is converted into the corresponding chlorin (VI) almost instantaneously. Treatment with methanolic cupric acetate afforded a purple copper derivative, the light-absorption maxima of which are recorded in Table 1. In presence of ammonia this derivative is partially dehydrogenated to copper octaethylchlorin.

The structure of the *a*-octaethyltetrahydroporphin is confirmed by spectroscopic and analytical data, and by the quantitative dehydrogenation (see below) of the metal-free pigment and of its copper complex to the corresponding chlorin derivatives.



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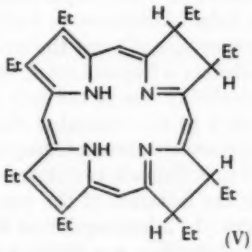

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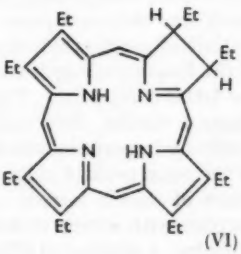

(VI)

b-*Octaethyltetrahydroporphin.*—The yellow fraction from the chromatogram showed an intense peak at 720 mμ indicating the presence of a pigment of " bacterio "-type. It was not pure, however, and when it was re-chromatographed on magnesium oxide in hexane traces of a yellow material of unknown constitution were separated from it. A purified *b*-octaethyltetrahydroporphin (IV) concentrate was obtained which was used in subsequent experiments. It exhibited a faint orange fluorescence which may have been due to traces of impurities. The yield of the pigment was less than 1% and no attempts were made to isolate it in the solid state. Its light-absorption properties are given in Table 1 and in Fig. 1. They bear a striking resemblance to those of bacteriochlorin e_6; [11] the spectrum of the latter compound shows a bathochromic shift of about 20—30 mμ, presumably due to the presence of a nuclear acetyl group in the 2-position. This fact, together with the quantitative dehydrogenation to octaethylchlorin (see below), are compelling evidence for the structure proposed.

In order to determine whether the reaction was general, the iron complexes of octamethyl- and ætio-porphin II were reduced under the same conditions. From the former, poor yields were obtained, chiefly owing to the low solubility of the pigment. *a*-Tetrahydro-octamethylporphin was, however, identified spectroscopically and by its characteristic orange fluorescence. In the case of the ætioporphyrin II it was possible to separate

[10] Fischer and Helberger, *Annalen*, 1929, **471**, 293.
[11] Golden and Linstead, unpublished results.

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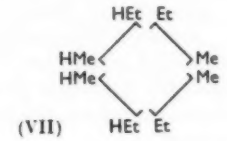
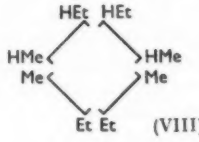
the products chromatographically. Ætiochlorin II and *a*-tetrahydroætioporphin II were isolated in good yield and identified spectroscopically. Traces of the *b*-tetrahydro-derivative were also present. The behaviour of the pigments on chromatography differed somewhat from those of the octaethyl series: the order of elution was the same but the pigments were adsorbed more strongly. It is interesting that the *a*-tetrahydroætioporphin II separated into two zones on chromatography. They were spectroscopically



(VII)



(VIII)

identical and furnished the same chlorin on dehydrogenation. Two positional isomers (VII) and (VIII) of *a*-tetrahydroætioporphin are theoretically possible and the two fractions may correspond to these.

During the preparation of unsubstituted chlorin [12] a red pigment with an orange fluorescence was obtained which was not further investigated at the time. In the light of the present results it seemed likely that it was *a*-tetrahydroporphin. In attempts to isolate it in a pure state, chromatography on magnesium oxide proved very slow and the pigment tended to be dehydrogenated on prolonged contact with the adsorbent. By developing the column with benzene for a short time and separating the bands mechanically the pigment was obtained pure. Its light absorption is included in Table 1: it corresponds to that of *a*-octaethyltetrahydroporphin (V) but the whole spectrum, with the exception of the long-wavelength band, exhibits a hypsochromic shift of about 5 mμ with respect to the latter compound. This is probably due to the lack of alkyl substituents since chlorin shows a similar shift with respect to the octaethyl derivative. The 637·5 mμ band of *a*-tetrahydroporphin, which is apparently chromatographically pure, is in the same position as the main peak of chlorin and it is difficult to determine whether it is genuine or due to traces of chlorin formed during the isolation of the pigment. Reaction of *a*-tetrahydroporphin with excess of tetrachloro-1 : 2-benzoquinone was very slow in the cold but, on warming, a mixture of chlorin and porphin was produced. When treated with methanolic cupric acetate, *a*-tetrahydroporphin afforded a copper derivative with absorption maxima at 547, 589, and 602·5 mμ. The last peak is presumably due to copper chlorin which may have been formed during the preparation of the copper derivative or from chlorin originally present in the *a*-tetrahydroporphin. Treatment of the above mixture of copper derivatives with tetrachloro-1 : 2-benzoquinone afforded copper chlorin which was identified spectroscopically.

Reduction of octaethylchlorin (VI) was next investigated. The first stage involved the preparation of the unknown iron complex of the chlorin (VI). Treatment of the pigment (VI) with ferric chloride and sodium acetate in boiling benzene, dioxan, pyridine, or acetic acid afforded only unchanged starting material, but ferrous chloride and sodium acetate in boiling acetic acid in an inert atmosphere afforded the desired product. It could not readily be crystallised and was used without purification. It and the corresponding iron octaethylporphin complex have broad and ill-defined maxima of low intensity (see Table 1) in contrast to the corresponding metal-free and copper derivatives.

Reduction of the iron octaethylchlorin in the usual manner and subsequent chromatography afforded unchanged starting material, *a*-octaethyltetrahydroporphin, traces (<1%) of the *b*-tetrahydro-derivative, and two new substances, namely octaethylhexa- (IX) and octaethylocta-hydroporphin (X).

Octaethylhexahydroporphin.—This material, a purple pigment, was separated from the

[12] Eisner and Linstead, *J.*, 1955, 3742.

a-tetrahydro-derivative (formed in roughly equal amount) on deactivated alumina but not on magnesium oxide. The purple pigment produced in the reduction of octaethylporphin was shown to be identical with octaethylhexahydroporphin. The pure hexahydro-derivative does not fluoresce although its solutions generally show a faint orange fluorescence due, presumably, to traces of the *a*-tetrahydro-derivative. It is very soluble in all organic solvents except methanol and acetone, and attempts at crystallisation failed. Its solutions are stable in the absence of light. Its absorption bands (Table 1; Fig. 2) are broad and

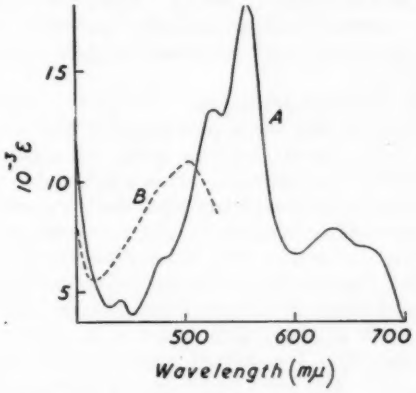


FIG. 2. *A, Octaethylhexahydroporphin. B, Octaethyloctahydroporphin.*

TABLE 1. *Light absorptions (in benzene).*

$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
a-Octaethyltetrahydroporphin				Bacteriochlorin e_6 [11]			
370 [a]	103,500	511	9,300	387 [a]	112,000	631	3,700
379·5 [a]	92,700	546	17,600	457	3,500	691	7,200
401	52,300	586	32,100	493	5,000	754	93,300
482	5,300	634	9,000	525	27,600		
Cu *a*-octaethyltetrahydroporphin				Octaethylhexahydroporphin			
391 [a]	208,000	550·5	12,800	355—357 [a]	43,600	527 [c]	13,100
532 [b]	8,800	594	60,000	436—440	4,600	557·5 [c]	18,100
α-Tetrahydroporphin				480 [b]	6,500	636	7,800
378 [a]	1·927 [e]	583	0·569	Octaethyloctahydroporphin			
500	0·194	637·5	0·285	339—349 [a]	38,400	500—505 [d]	10,900
541	0·326			Fe octaethylchlorin			
b-Octaethyltetrahydroporphin				380 [a]	98,400	604	12,400
374 [a]	180,700	604	2,500	525—529	7,600	655—658	18,200
434	9,200	661·5	6,200	Fe octaethylporphin			
463	20,300	685	14,100	375 [a]	90,000	534·5	10,500
491	49,300	721	150,000	395—398 [b]	71,800	632·5	5,500
				517	9,200		
				Cu octaethylporphin			
				399 [a]	364,000	562·5	30,600
				525·5	14,200		

[a] Soret band. [b] Inflection. [c] $\lambda_{max.}$ 519—522 mμ and 552—554 mμ in *cyclo*hexane; 518—520 mμ and 552 mμ in *n*-hexane. [d] $\lambda_{max.}$ at 491 mμ in light petroleum. [e] Arbitrary *E* values.

ill-defined, particularly in benzene, with relatively low intensities, and are subject to considerable solvent influence. The whole spectrum in benzene is bathochromically shifted by about 5 mμ from that observed in *n*-hexane or *cyclo*hexane. Calvin and Seely [6] pointed out that although the conjugation of the macrocyclic system in a hexahydroporphin is formally interrupted, several resonance forms may be drawn; this is not possible

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in the case of an octahydroporphin. Consequently we should expect the spectrum of the former, but not of the latter, to resemble that of a porphyrin, which in fact it does.

Treatment of a boiling benzene solution of octaethylhexahydroporphin with methanolic cupric acetate afforded copper *a*-octaethyltetrahydroporphin quantitatively. When a warm solution of octaethylhexahydroporphin was treated with methanolic zinc acetate, a colour change to bluish-green took place with the appearance of a broad absorption peak at 652 mμ. Almost instantaneously, however, this began to disappear and its place was taken by a new peak at 598 mμ. The latter is due to the *a*-tetrahydro-derivative, as shown by its occurrence with an authentic specimen. The qualitative absorption data of the zinc complexes of octaethyl- and *meso*tetraphenyl-porphin and their hydro-derivatives are given in Table 2.

Octaethyloctahydroporphin.—The first fraction in the chromatographic separation of the reduction product was a pink pigment with a single absorption peak at 491 mμ (in light petroleum). It was not very stable and could not be obtained free from traces of the *a*- and *b*-tetrahydroporphins. This was not due to imperfect separation as the bands were well-defined and completely separated from each other. On spontaneous evaporation of the concentrated solution in light petroleum at 0° and in the absence of light, the corresponding di-, tetra-, and hexahydro-derivatives, separable by chromatography, were formed. The spectrum of the purified concentrate of octaethyloctahydroporphin (which still contained traces of the two tetrahydro-derivatives) is given in Table 1 and Fig. 2. The single peak in the visible region is in agreement with the interrupted conjugation of structure (X). The solvent effect is even more pronounced than for the hexahydro-derivative. The Soret band shows a hypsochromic shift with respect to the other hydro-derivatives; the wavelengths of the Soret bands in the series decrease in the order porphin > chlorin > *b*-tetrahydro > *a*-tetrahydro > hexahydro > octahydro. The number of " extra " hydrogen atoms is confirmed by quantitative dehydrogenation (see below). Their position cannot at present be determined. Hydrogen may be added to the 2 : 3-positions of a pyrrole nucleus as in (Xa) or to the 2 : 5-positions as in (Xb). The addition of hydrogen to the *meso*-positions of the porphyrin system is also a possibility.

TABLE 2. *Absorption maxima* (mμ) *of zinc complexes* (*in benzene*).

Series	Porphin	Chlorin	*a*-Tetrahydro	Hexahydro
Octaethyl	536, 573	617	598, 553	652
*meso*Tetraphenyl	549, 587	618	602	642

Determination of Hydrogenation Level by Quantitative Dehydrogenation.—An excess of tetrachloro-1 : 2-benzoquinone converts *a*-octaethyltetrahydroporphin in benzene into the chlorin. When carried out quantitatively (cf. Eisner and Linstead [13]), the reaction was relatively slow at room temperature, being complete only after about 70 hr. The chlorin (VI) was not dehydrogenated under these conditions. When 1 mol. of freshly sublimed quinone in carefully dried benzene was used a 90% yield of chlorin was obtained. With 0·5 mol. of quinone the yield was about 50%.

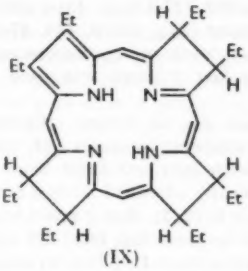
The copper derivative of *a*-octaethyltetrahydroporphin was dehydrogenated almost instantaneously to the copper chlorin complex under the same conditions and the yield of the latter was quantitative with 1 mol. of quinone. When 2 mols. of quinone were used, slow dehydrogenation to the copper porphin took place. The yield of the latter was 57% after 71 hr. and reached a limiting value of 76% after 428 hr. The light absorption of the known copper octaethylporphin, which was prepared by standard methods, is given in Table 1.

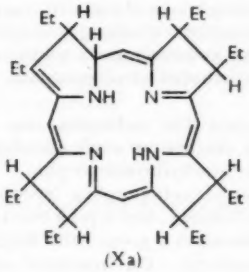
b-Octaethyltetrahydroporphin with a slight excess of the quinone afforded octaethylchlorin. The concentration of the pigment, and hence its ε values, was calculated from the amount of chlorin produced. *b*-Octaethyltetrahydroporphin with 1 mol. of quinone

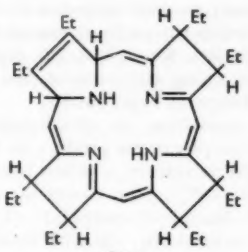
[13] Eisner and Linstead, *J.*, 1955, 3749.

afforded 78·2% of chlorin after 70 min., and 96·6% after 18 hr., whereas the figures for the *a*-tetrahydro-compound were 55·3% after 3 hr. and 67·4% after 20 hr.

It was not possible to obtain quantitative data for the dehydrogenation of octaethylhexahydroporphin. It could be shown qualitatively that a deficiency of the quinone gave only *a*-octaethyltetrahydroporphin, with traces of the chlorin. The main absorption peaks


(IX)


(Xa)


(Xb)

of the hexahydro- and *a*-tetrahydro-pigments overlap in such a way that it is very difficult to calculate their concentrations in presence of each other. Further, dehydrogenation was very slow and excess of the quinone did not afford the chlorin quantitatively. The action of 2 : 3-dichloro-5 : 6-dicyanobenzoquinone was next investigated. With a slight excess, chlorin was produced quantitatively and the concentration and ε values of octaethylhexahydroporphin could be calculated. Dehydrogenation with this quinone was instantaneous and the addition of 2 mols. afforded the chlorin (VI) in 100% yield. An excess (3 mols.) gave about 80% octaethylporphin whereas a deficiency (0·5 and 1 mol.) afforded mixtures of the chlorin (VI), the *a*-tetrahydroporphin (V), and, presumably, unchanged starting material. No *b*-octaethyl-tetrahydroporphin could be detected at any stage. The purity of the quinone used was determined by dehydrogenation of a solution of octaethylchlorin of known concentration under standard conditions.

The dehydrogenation of octaethyloctahydroporphin with the dichlorodicyanoquinone was carried out in the same way as for the hexahydro-derivative and results were comparable: 3 mols. of quinone afforded the chlorin (VI) quantitatively; 4 mols. afforded octaethylporphin (80%), and 1 and 2 mols. produced a complex mixture in which octaethylchlorin and the *a*-tetrahydro-derivative were identified.

Experimental

Unless otherwise stated, light petroleum had b. p. 60—80°.

Reduction of Octaethylporphin.—The procedure has been described previously.[9] Chromatography of the product on heavy magnesium oxide with light petroleum eluted a yellow band of crude *b*-octaethyltetrahydroporphin followed by a pink band of *a*-octaethyltetrahydroporphin. The first runnings of the latter band contained traces of octaethylhexahydroporphin. Benzene–light petroleum (1 : 1) eluted octaethylchlorin (32·5%) preceded by a pink fraction which was spectroscopically identical with *a*-octaethyltetrahydroporphin. The pink fraction could not be obtained free from the chlorin. Ether–chloroform (1 : 1) eluted a green band which was spectroscopically similar to octaethylchlorin. Chloroform removed some unchanged starting material.

a-*Octaethyltetrahydroporphin.*—The pigment was dissolved in dry methanol and the solution was concentrated to ~1 c.c. in a current of nitrogen. On cooling to −80° or storage at 0° deep red needles of a-*octaethyltetrahydroporphin*, m. p. 138°, separated (Found: C, 80·3, 80·5; H, 9·2, 9·5; N, 9·8, 9·7. $C_{36}H_{50}N_4$ requires C, 80·25; H, 9·35; N, 10·4%).

Copper a-*Octaethyltetrahydroporphin.*—A solution of *a*-octaethyltetrahydroporphin in boiling

benzene was treated with a slight excess of cupric acetate in methanol in a current of nitrogen. The purple solution was cooled, washed with water, and concentrated under reduced pressure, and its light absorption was determined immediately. When the solution was washed with dilute ammonia solution instead of water, a mixture of copper *a*-octaethyltetrahydroporphin and copper octaethylchlorin was produced.

b-*Octaethyltetrahydroporphin.*—The crude pigment was chromatographed in *n*-hexane on heavy magnesium oxide. The following fractions were collected: (i) a pale pink solution with a faint greenish fluorescence containing traces of pigment ($\lambda_{max.}$ 380, 509, 727·5 mμ); (ii) a yellow solution with a faint orange fluorescence containing traces of pigment ($\lambda_{max.}$ 379·5, 435, 470—475, 501, 659·5, 680, 721 mμ); (iii) yellowish-green solution with a weak orange fluorescence containing the bulk of the *b*-octaethyltetrahydroporphin. This last fraction was used in subsequent experiments.

Reduction of Ætioporphyrin II.—The reduction was carried out as before. Chromatography of the product on heavy magnesium oxide afforded the following fractions: (1) with light petroleum, a yellow band of *b*-tetrahydroætioporphin; (2, 3) with light petroleum–benzene (10—40%), pink bands of *a*-tetrahydroætioporphin (spectroscopically identical with *a*-octaethyltetrahydroporphin); (4) with benzene, first a pink band similar to (2, 3), then a green band of ætiochlorin; (5) with ether–chloroform a green band similar to the preceding one; (6) with chloroform a red band of ætioporphyrin. On treatment with tetrachloro-1 : 2-benzoquinone bands 2, 3 afforded ætiochlorin.

Purification of a-*Tetrahydroporphin.*—The crude pigment, whose preliminary purification has been described,[12] was extracted with boiling methanol, and the insoluble residue was chromatographed in benzene on heavy magnesium oxide. Elution with benzene did not completely separate the chlorin and the tetrahydroporphin. The fraction containing the bulk of the red *a*-tetrahydroporphin was evaporated to dryness under reduced pressure, dissolved in benzene, and re-chromatographed on heavy magnesium oxide. Elution with benzene was continued for 3 hr., whereby the bands of chlorin and *a*-tetrahydroporphin were separated. The column was then drained and extruded, the *a*-tetrahydroporphin fraction separated, suspended in cold chloroform, and filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in benzene and the light absorption was determined. A warm benzene solution of *a*-tetrahydroporphin with excess of tetrachloro-1 : 2-benzoquinone gave a mixture of chlorin and porphin.

Reduction of Octaethylchlorin.—Ferrous chloride (200 mg.) and anhydrous sodium acetate (400 mg.) in boiling acetic acid (8 c.c.) were treated with octaethylchlorin (90 mg.) in acetic acid (2 c.c.), boiled under nitrogen for 5 min., then cooled, and benzene (150 c.c.) was added. The solution was washed with water, ammonia solution, and water, and evaporated to dryness under reduced pressure. Attempted crystallisation from light petroleum–methanol failed. The crude iron complex was treated in boiling *iso*pentyl alcohol (15 c.c.) with sodium (1·6 g.) in a current of nitrogen. The product, which was worked up in the usual manner, was chromatographed on heavy magnesium oxide. Elution with light petroleum removed successive bands of (pink) octaethyloctahydroporphin, (yellow) *b*-octaethyltetrahydroporphin, and (purple and then pink) octaethyl-hexa- and -(*a*)tetra-hydroporphin. Benzene finally eluted octaethylchlorin (green).

Octaethylhexahydroporphin. The material obtained from the purple fraction was chromatographed in *n*-hexane on alumina (Grade IV; deactivated with methanol). Elution with *n*-hexane gave good separation of the *a*-tetrahydro- (eluted first) and the hexahydro-pigment. The latter formed deep purple solutions in organic solvents. It was sparingly soluble in acetone and insoluble in methanol but did not crystallise. Its solution in boiling benzene with methanolic cupric acetate gave copper *a*-octaethyltetrahydroporphin quantitatively. Zinc octaethylhexahydroporphin was formed from a hot benzene solution of the metal-free pigment by methanolic zinc acetate; it reverted almost immediately to the corresponding *a*-tetrahydro-derivative.

Octaethyloctahydroporphin. A solution of the pigment obtained in the first pink fraction was kept in the dark at 0° for several weeks, then rechromatographed on magnesium oxide with *n*-hexane as eluant; the first fraction consisted of octaethyloctahydroporphin containing traces of the two tetrahydro-derivatives. Octaethylhexahydroporphin and octaethylchlorin were eluted separately from the column and were identified spectroscopically.

Copper Octaethylporphin.—Octaethylporphin was extracted from a thimble into boiling

acetic acid containing excess of cupric acetate. The extract was cooled, and the copper derivative filtered off and chromatographed on alumina with benzene as eluant. After two crystallisations from benzene, copper octaethylporphin was obtained in red needles (Found: C, 72·2; H, 7·7; Cu, 10·4. Calc. for $C_{36}H_{44}N_4Cu$: C, 72·5; H, 7·4; Cu, 10·7%).

Quantitative Dehydrogenation.—The method has been described.[13] Experiments were carried out in benzene in the dark in 5 c.c. volumetric flasks. Spectroscopic measurements were made in 1 cm. stoppered cells. 2 : 3-Dichloro-5 : 6-dicyanobenzoquinone was standardised by allowing a benzene solution of known concentration to react with an excess of a benzene solution of octaethylchlorin of known concentration. Its purity was thus found to be 84·5%. Unless otherwise stated the yields of a pigment calculated from the intensities at a certain wavelength have not been corrected for the presence of other pigments since the spectral regions chosen were such as to minimise any interference.

Freshly sublimed tetrachloro-1 : 2-benzoquinone and benzene distilled from sodium were used. The following results were obtained:

a-*Octaethyltetrahydroporphin.*

Time (hr.)	Quinone (mols.) 0·5	1	2	Quinone (mols.) 0·5	1	2
	Chlorin formed (%)			Unchanged tetrahydro (%)		
3	32	52	83·5	67	45	15
72	49	91	94	53	10	5
116	48	90	90	53	10	5

Copper a-*octaethyltetrahydroporphin.*

Time (hr.)	0·5 mol. of quinone: Unchanged Cu *a*-tetrahydro	Quinone (mols.) 0·5	1	2	2 mols. of quinone: Cu porphin formed (%) 527 mμ	563 mμ
			Cu chlorin formed (%)			
0·25	47	56 *	100	99	—	—
71	46	59 *	96	48	53	57
116	45	61 *	96·5	37	57·5	64
284	—	—	98	26	66	74
428	—	—	—	23	67	76

* Corr. for Cu *a*-octaethyltetrahydroporphin.

b-*Octaethyltetrahydroporphin.*

Time (hr.)	Quinone (mols.) 0·5	1	2	Quinone (mols.) 0·5	1	2
	Chlorin formed (%)			Unchanged *b*-tetrahydro (%)		
1·2	45·6	78·2	99·0	57·2	24·0	1·2
18	49·1	96·6	100	51·1	2·2	—

Octaethylhexahydroporphin. Quantitative results could not be obtained with tetrachloro-1 : 2-benzoquinone. When an insufficiency of quinone was added, *a*-octaethyltetrahydroporphin with only traces of the corresponding chlorin were produced. The reaction required 3 days for completion. Using 2 : 3-dichloro-5 : 6-dicyanobenzoquinone and making measurements immediately after mixing showed 43, 100, and 18% of chlorin formed with 1, 2, and 3 mols., respectively, of quinone: and with 3 mols. of quinone, 83·5% (532 mμ) or 79% (568 mμ) of porphin was formed.

Octaethyloctahydroporphin. The procedure was that used for the hexahydro-derivative. With 1, 2, 3, and 4 mols. of quinone the amount of chlorin formed was 25, 61, 100, and 31% respectively. With 4 mols. of quinone, 80·5% (532 mμ) or 73% (568 mμ) of porphin was formed.

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Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

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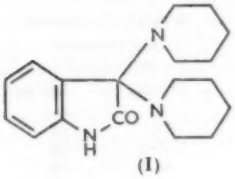
XUM

691. *The Structure of Isatin Blue.*

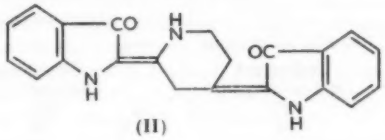
By A. W. Johnson and D. J. McCaldin.

New structures are suggested for isatin blue and the related compounds derived by condensation of isatin with either cyclic secondary bases or cyclic α-imino-carboxylic acids.

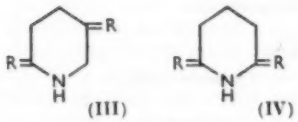
Proline [1] and several related compounds [2,3] are frequently characterised by the deep blue colours they give with solutions of isatin. The product from the reaction of proline and isatin can be isolated as deep blue crystals, and is identical with the condensation product from pyrrolidine and isatin in hot acetic anhydride; [4,5] likewise pipecolic acid in aqueous solution, and piperidine in acetic anhydride, both condense with isatin to give the so-called isatin blue which is closely related to the isatin–proline product. Isatin blue is noteworthy for the variety of structural formulæ, all of which are now shown to be incorrect, proposed for it since its discovery in 1891 by Schotten.[6] He prepared the compound by heating 3 : 3-dipiperidino-oxindole (I) ("isatin dipiperidide"; the position of the piperidino-groups was not known at that time) either alone or, better, with acetic anhydride, and he showed that 1·5 mols. of piperidine were eliminated from each mol. of the dipiperidide during the reaction. The correct molecular formula, $C_{21}H_{17}O_2N_3$, was thereby deduced for isatin blue which is thus derived from two mols. of isatin and one of piperidine; but Schotten was unable to suggest a structural formula for the compound.



(I)

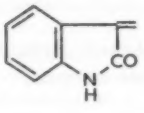


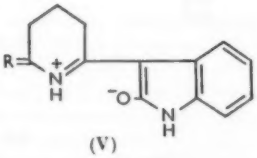
(II)



(III) (IV)

R =





(V)

Isatin blue was next studied by Liebermann and Krauss [7] who showed that it formed a red hydrochloride and that related compounds could be obtained from piperidine and bromo- or chloro-isatin, but not from *N*-substituted piperidines and isatin. On this additional evidence and no doubt influenced by the structure of indigo, they proposed 2 : 4-di-(2-indoxylylidene)piperidine (II) as the structure of isatin blue. Apart from the lack of a convincing mechanism of formation, formula (II) is untenable for several reasons: it does not account for the blue colour; pyrrolidine and morpholine, known to give blue condensation products with isatin, contain no carbon atom equivalent to the 4-C of piperidine; and neither isatin 3-oxime nor 3 : 3-ditolyloxindole condenses with piperidine to give isatin blue.[4] In 1924, Heller [8] reconsidered the earlier work and rejected structure

[1] Acher, Fromageot, and Jutisz, *Biochim. Biophys. Acta*, 1950, **5**, 81.
[2] Zacharius, Thompson, and Steward, *J. Amer. Chem. Soc.*, 1952, **74**, 2949.
[3] Hulme *et al.*, *Nature*, 1952, **170**, 659; 1954, **173**, 588; **174**, 1055.
[4] Grassmann and Arnim, *Annalen*, 1934, **509**, 288.
[5] *Idem*, *ibid.*, 1935, **519**, 192.
[6] Schotten, *Ber.*, 1891, **24**, 1366, 2604.
[7] Liebermann and Krauss, *ibid.*, 1907, **40**, 2492; see also Liebermann and Häse, *ibid.*, 1905, **38**, 2847.
[8] Heller, *Z. angew. Chem.*, 1924, **37**, 1017; *Chem. Ztg.*, 1930, **54**, 985; 1933, **57**, 74.

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(II) in favour of 2 : 5-di-(3-oxindolylylidene)piperidine (III) which is quoted in certain recent reviews of isatin chemistry;[9] but, like (II), structure (III) contains no chromophoric system capable of accounting for the intense colour of isatin blue and consequently also must be discounted. The most extensive work on these pyrrolidine and piperidine colouring matters is that of Grassmann and Arnim [4,5] who confirmed the earlier observation that the compounds could not be formed from the *N*-substituted bases and concluded that the pigments were best represented by structures of type (IV).

We were attracted to the problem because the formation of (IV) from (I) would involve a double condensation or rearrangement involving the α-carbon atoms of piperidine, and such condensations are of very limited occurrence.[10] The analogy drawn by the German authors [5] with migrations from nitrogen to carbon in the pyrrole series is clearly invalid. Structure (IV) may be regarded also as the zwitterion (V) which contains an extended conjugated system consistent with the absorption in the visible spectrum. In considering this possibility we showed that analogues (spectra: Table 1) of isatin blue could be produced from a variety of bases including 4-hydroxyproline,[4] morpholine, 2- and 3-methylpiperidine, and *cis*-octahydroindole. The formation of coloured products from 2-substituted piperidines and *cis*-octahydroindole was incompatible with structures (IV) and (V), and in addition the infrared spectrum of the blue product derived from *N*-methylisatin and pyrrolidine showed no bands between 3450 and 2300 cm.$^{-1}$ corresponding to $\rangle$NH or $\rangle\overset{+}{\text{N}}$H.[11] On this evidence, coupled with the observation that the *N*-substituted bases do not give coloured compounds with isatin, it appears that the nitrogen atom of the base is attached directly to one of the isatin fragments in isatin blue, and consequently structures (III), (IV), and (V) must be rejected.

Examination of the spectra of isatin blue and its analogues (Table 1*a*) shows that substitution of pyrrolidine for piperidine rings causes a lowering of the position of the long-wavelength band probably because of steric effects and the introduction of an extra band(s) at *ca.* 330 mμ. Several features of the spectra suggest that substitution at the 3-position of the bases has a more pronounced effect than the corresponding substitution at position 2, *e.g.*, the band at 260 mμ disappears altogether in the spectra of the coloured products derived from 3-methylpiperidine (contrast the 2-methyl isomer), and the introduction of the cyclic oxygen atom (a $C_{(3)}$-substituent) in morpholine has a pronounced hypsochromic effect on the spectrum of the derived pigment. Furthermore the blue compound from 2-methylpiperidine and isatin was obtained without difficulty in high yield (78%), whereas the corresponding product from 3-methylpiperidine could be obtained only in very poor yield (3·5%). These observations, which suggest that it is the 3-positions of the cyclic bases which are involved in the condensation reactions, have led us to propose a resonance hybrid of structures (VI) and (VII) for isatin blue.

The dipiperidide (I) is the first intermediate in the reaction between isatin and piperidine and it can be isolated and converted into isatin blue as observed by Schotten.[6] The experimental conditions are such as to cause the loss of piperidine from this intermediate, to yield the cation (VIII). Activation of the 3-position of the piperidine ring is caused by the electronic shifts shown which give rise to a potential double bond between the nitrogen and $C_{(3)}$ of the piperidine ring. Condensation of the ion (VIII) with a second molecule of the intermediate (I) then gives the hybrid (VI–VII) with elimination of two further molecules of piperidine. The existence of at least one intermediate between (I) and (VI) is substantiated by the formation of transitory green colours during the reaction. Oxidation of isatin blue under various conditions has given isatin, anthranilic acid, and picric acid, but no significant products corresponding to the original base have been isolated.

[9] Sumpter, *Chem. Rev.*, 1944, **34**, 425; "The Chemistry of Heterocyclic Compounds. Indole and Carbazole Systems," Interscience Publ. Inc., 1954, p. 132; Elderfield, "Heterocyclic Compounds," Wiley, 1952, Vol. III, p. 230.
[10] Cf. Huisgen and Rist, *Annalen*, 1955, **594**, 161; Wittig and Ludwig, *ibid.*, 1954, **589**, 58.
[11] Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.

Pyrolysis of the colouring matter from isatin and pyrrolidine has yielded oxindole. This degradation, which recalls both the Hofmann degradation and the Wolff–Kishner reduction, provides further evidence in support of a chromophore containing an *N*-substituted piperidine as in (VII).

TABLE 1. *Spectra of isatin blue and related compounds.*

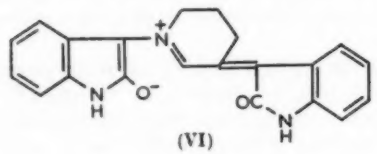
(a) *In* NN-*dimethylformamide.*

Pigment	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
Piperidine–isatin (or pipecolic acid–isatin)	260	4·09	295	4·12		—	472	3·74	635	4·60
2-Methylpiperidine–isatin ...	260	4·05	294	4·15		—	476	3·71	635	4·57
Morpholine–isatin	261	4·03	287	4·16		—	458	3·87	600	4·64
3-Methylpiperidine–isatin ...		—	294	4·11		—	473	3·74	635	4·63
Pipecolic acid–acenaphthenequinone		—	290	4·22		—	405 489	3·69 3·77	650	4·64
Pyrrolidine–isatin (or proline–isatin)	263	3·99	283	3·96	325	3·79	440	3·77	596	4·68
Octahydroindole–isatin		—	287	3·96	327 340	3·70 3·68	452	3·77	615	4·63
β-Hydroxyproline–isatin [5]	260	3·95	285	3·93	330	3·65	455	3·72	610	4·55
Pyrrolidine–*N*-methylisatin	261	4·00		—	325 338	3·73 3·73	459	3·87	592	4·69
Proline–acenaphthenequinone [5]		—	299	4·14		—	385 490	3·63 3·62	615	4·53
*iso*Indoline–isatin	260	4·20		—	337	3·85	423 445 534	3·90 3·90 4·20	660 830	3·90 3·44

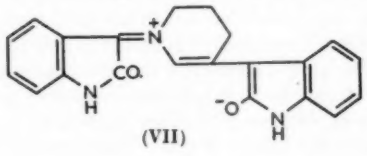
(b) *In* 5N-*hydrochloric acid.*

Piperidine–isatin	207	4·56	263	4·36	371	4·28	488	3·41		
2-Methylpiperidine–isatin	211	4·51	260	4·31	370	4·28	500	3·38		
Morpholine–isatin	209	4·49	262 298	4·29 3·90	412	4·13	510	3·00		
3-Methylpiperidine–isatin	210	4·45	263	4·26	385	4·26	496	3·34		
Pipecolic acid–acenaphthenequinone (in 11N-HCl)	219 238	4·88 4·66	331	4·56		—	477	3·76		
Pyrrolidine–isatin	211	4·51	262	4·28	382	4·28	484	3·46		
Octahydroindole–isatin	211	4·51	261	4·21	384	4·21	498	3·42		
Pyrrolidine–*N*-methylisatin	210	4·57	270	4·25	380	4·28	482 495	3·22 3·23		

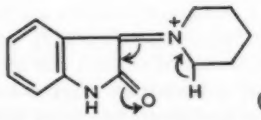
Some of the observations of Grassmann and Arnim[4,5] are not in accord with a general structure of type (VI) (or VII) for the isatin blue series and, in particular, certain cyclic bases containing both β- and β′-substituents were claimed to give coloured products related



(VI)



(VII)



(VIII)

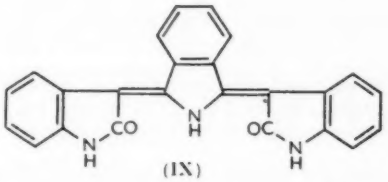
to isatin blue. These included 4-ethyl-3-methylpyrrolidine (prepared by hydrogenation of opsopyrrole; no details given), but as no pure product was isolated from the condensation no great emphasis can be placed on the observation, especially as isatin is known to give other series of coloured products with heterocyclic bases.[12] *iso*Indoline condensed with

[12] Grassmann and Arnim, *Annalen*, 1936, **522**, 66.

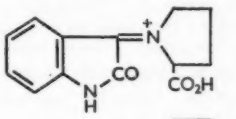
isatin to give a coloured product, which was claimed [5] to have the structure (IX) by analogy with isatin blue. This preparation has been repeated and the product, obtained in poor yield, shown to have properties quite different from those of isatin blue, especially the absorption spectrum (Table 1) and the blue solution given in concentrated sulphuric acid (isatin blue gives a red solution which changes to blue after neutralisation). The true nature of the product has not been determined but as it does not belong to the isatin blue series, it no longer presents an anomaly.

Reference should also be made to bases which might have been expected to yield coloured condensation products of the isatin blue type with isatin but in fact did not. These included 2 : 6-dimethylpiperidine and *trans*-decahydroquinoline (neither of which gave a 3 : 3-diamino-oxindole derivative probably for steric reasons), and various partly reduced pyridines, *e.g.*, tetrahydroquinoline and indoline which gave substituted 3 : 3-diamino-oxindoles that were stable to heat, tetrahydro*iso*quinoline which gave a coloured product,[5] not in the isatin blue series, and baikiain,[13] 1 : 2 : 3 : 6-tetrahydropicolinic acid, which gave no recognisable product.

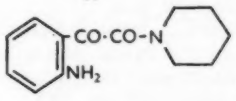
In the ready reaction of proline and other cyclic α-imino-acids with isatin, the decarboxylation is visualised as occurring with the intermediate (X) which is a " vinylogue " of a β-keto-acid and thus readily loses carbon dioxide.



(IX)



(X)



(XI)

In the course of the work, a variety of 3 : 3-diamino-oxindoles (*e.g.*, I) (spectra : Table 2) were prepared from isatins and cyclic secondary amines, preferably by an azeotropic distillation method [14] or alternatively from the isatin β-anils. We have shown that the equimolecular condensation products from isatin and amines are isatamides (*e.g.*, XI) (spectra : Table 3) and are not concerned in the formation of the isatin blue colouring matters, in agreement with the suggestions of earlier workers.[6,7]

TABLE 2. *Spectra of the substituted* 3 : 3-*diamino-oxindoles* (e.g., I) (*isatin* + 2 *mols. of base*) *in methanolic solution.*

Base	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
Piperidine	209	4·15	250	3·82	292	3·28
Morpholine	209	4·43	252	3·78	292	3·23
Tetrahydroquinoline	211	4·90	261	4·38	—	
Tetrahydro*iso*quinoline	207	4·65	254	4·02	289	3·49
Pyrrolidine	211	4·39	244 248	4·30 4·31	298	3·56
Indoline	208	4·74	263	4·44	—	

It seems probable that cyclic secondary amines and the corresponding α-carboxylic acids will condense with a variety of cyclic α-diketones and *o*-quinones to give coloured products related to isatin blue. We have confirmed the observation by Grassmann and Arnim [5] that a crystalline coloured product can be obtained from acenaphthenequinone and proline and unlike the German workers we have been able to obtain the analogous

[13] King, King, and Warwick, *J.*, 1950, 3590.
[14] Herr and Heyl, *J. Amer. Chem. Soc.*, 1953, **75**, 1918.

XUM

compound from pipecolic acid. The similar reactions with ninhydrin have an obvious bearing on the blue colours derived from α-amino-acids and are under investigation.

TABLE 3. *Spectra of substituted isatamides* (e.g., XI) (*isatin* + 1 *mol. of base*) *in methanolic solution.*

	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
5-Bromoisatin–piperidine	203	4·32	239	4·40	264	3·89	392	3·82
5-Bromoisatin–morpholine		—	231	4·39	264	3·87	395	3·80
5-Bromoisatin–hexamethyleneimine		—	230	4·38	264	3·88	393	3·80
N-*Acetyl derivatives* :								
Isatin–piperidine	202	4·30	235	4·44	267	4·04	339	3·76
Isatin–morpholine	201	4·41	239	4·53	266	3·76	352	3·70
5-Bromoisatin–piperidine		—	240	4·45	266	4·03	355	3·64
5-Bromoisatin–morpholine		—	240	4·48	266	4·04	355	3·63
5-Bromoisatin–hexamethyleneimine		—	240	4·48	265	4·07	353	3·70

EXPERIMENTAL

Preparation of 3 : 3-*Diamino-oxindoles.*—3 : 3-*Dipiperidino-oxindole.* (*a*) Isatin and piperidine were caused to react in warm alcoholic solution (method A) or under anhydrous conditions (method B; Herr and Heyl [14]). Isatin (10 g.) was suspended in dry benzene (250 c.c.) and heated under reflux in a Dean and Stark apparatus until all water had been removed. Dry piperidine (22 g.) was then added and the heating continued for 10 min., a further 0·9 c.c. of water (theor. for 1 mol., 1·2 c.c.) being collected. On cooling, the product crystallised as colourless plates, and was separated, washed with benzene and ethanol, and dried (9·3 g., 45%) (Found : C, 71·7; H, 8·25. Calc. for $C_{18}H_{25}ON_3$: C, 72·2; H, 8·4%). Above 100°, the product was converted into isatin blue.

(*b*) (Method C) : Isatin β-*p*-nitroanil [15] (500 mg.) and piperidine (1·5 c.c.) were shaken in ethanol (5 c.c.) and xylene (45 c.c.) at room temperature for 3 hr. The ethanol was removed under reduced pressure and the remaining solution cooled; the product crystallised and was separated as before (350 mg., 64%).

3 : 3-*Dipyrrolidino-oxindole.* This was best prepared by method C from isatin β-anil (1 g.) and pyrrolidine (5 g.) in methanol (2 c.c.) and xylene (48 c.c.). The colourless crystalline *product* (985 mg., 82%) so obtained liberated pyrrolidine and became bright blue at about 100° (Found : C, 70·6; H, 7·6; N, 15·3. $C_{16}H_{21}ON_3$ requires C, 70·8; H, 7·8; N, 15·5%).

3 : 3-*Dimorpholino-oxindole.* Prepared by method C from isatin β-anil (500 mg.) and morpholine (1·5 c.c.) as above, the colourless *product* (400 mg., 61%) was washed, dried, and crystallised from methanol and was rather more stable than the piperidino- or pyrrolidino-analogues (Found : C, 63·1; H, 7·0; N, 13·4. $C_{16}H_{21}O_3N_3$ requires C, 63·35; H, 7·0; N, 13·8%). Above 120° the product decomposed with formation of the corresponding blue product.

3 : 3-*Di*-(1 : 2 : 3 : 4-*tetrahydro*-1-*quinolinyl*)*oxindole.* Prepared by method A, the *product* (44%) formed colourless prisms, m. p. 296—298°, on crystallisation from methanol (Found : C, 78·6; H, 6·3; N, 10·5. $C_{26}H_{25}ON_3$ requires C, 78·95; H, 6·4; N, 10·6%).

3 : 3-*Di*-(1 : 2 : 3 : 4-*tetrahydro*-2-iso*quinolinyl*)*oxindole.* Prepared by method A, the *product* (19%) formed colourless prisms (from ethanol) which darkened above 200° and had m. p. 268—270° (decomp.) (Found : N, 10·5. $C_{26}H_{25}ON_3$ requires N, 10·6%). Solutions in hot methanol were purple but became colourless on cooling.

3 : 3-*Di-indolino-oxindole.* Prepared from isatin (0·5 g.) and indoline [16] (1·1 g.) by method A, the *product* (0·2 g.) formed colourless prisms, m. p. 204—206° (from methanol) (Found : N, 11·2. $C_{24}H_{21}ON_3$ requires N, 11·4%).

Isatin Blue.—(i) *From* 3 : 3-*dipiperidino-oxindole.* The product was prepared according to Schotten [6] by the action of acetic anhydride on 3 : 3-dipiperidino-oxindole at 60°. The reaction mixture was cooled, and the isatin blue separated and then crystallised slowly from methanol by a hot-extraction method (48 hr. for 500 mg.). The product was thus obtained as blue prisms with a green metallic sheen which had m. p. 230° (decomp.) (Found : C, 73·4; H, 5·05; N, 12·1. Calc. for $C_{21}H_{17}O_2N_3$: C, 73·45; H, 5·0; N, 12·2%).

[15] Angyal, Bullock, Hanger, Howell, and Johnson, *J.*, 1957, 1592.
[16] King, Barltrop, and Walley, *J.*, 1945, 277.

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(ii) *From* L-*pipecolic acid.* The acid (150 mg.) and isatin (300 mg.) were heated in ethanol (15 c.c.) under reflux for 30 min. The green mixture was cooled and the crystalline product (80 mg., 23%) separated and was washed with ethanol and ether. It crystallised from hot methanol as before (Found: C, 73·2; H, 4·8; N, 12·2%).

An attempted condensation of isatin and L-pipecolic acid according to the method of Grassmann and Arnim [5] gave *N*-acetylisatin as the main product.

Analogues of Isatin Blue.—(i) *From pyrrolidine.* Isatin (440 mg.) and pyrrolidine (100 mg.) were warmed with 2N-acetic acid (25 c.c.) on the steam-bath for ½ hr. After cooling, the resulting solution deposited the product as glistening green crystals (304 mg., 66%) which were separated, washed, and crystallised from methanol by the hot-extraction method (Found: C, 72·8; H, 4·7; N, 12·8. Calc. for $C_{20}H_{15}O_2N_3$: C, 72·9; H, 4·6; N, 12·8%).

(ii) *From* L-*proline.* Isatin (650 mg.) and L-proline (255 mg.) were suspended in phosphate buffer solution (50 c.c. at pH 7) and the mixture boiled for 15 min. The insoluble product (181 mg.) was separated from the solution, washed with hot water, ethanol, and ether, and crystallised from methanol as before; it formed glistening green crystals (80 mg., 23%) which showed an ultraviolet and visible spectrum identical with that of the product obtained from pyrrolidine.

(iii) *From morpholine.* 3 : 3-Dimorpholino-oxindole (2·5 g.) was suspended in a mixture of xylene (25 c.c.) and acetic anhydride and heated under reflux for 30 min. The green product was cooled and the precipitated coloured *compound* separated and washed with xylene, ethanol, and ether. It was then crystallised from methanol by the hot-extraction method to yield blue prisms (600 mg., 43%) with a green metallic lustre (Found: C, 69·6; H, 4·6; N, 12·1. $C_{20}H_{15}O_2N_3$ requires C, 69·6; H, 4·4; N, 12·2%).

(iv) *From 2-methylpiperidine.* Isatin (500 mg.) was suspended in a mixture of xylene (10 c.c.) and 2-methylpiperidine (500 mg.; b. p. 118—121°, prepared by hydrogenation of purified 2-picoline over Raney nickel at 200°/150 atm.) and heated under reflux for 4 hr. The blue *pigment* (460 mg., 78%) was isolated and purified by crystallisation from hot methanol, as blue prisms (Found: C, 73·6; H, 5·35; N, 11·6. $C_{22}H_{19}O_2N_3$ requires C, 73·9; H, 5·35; N, 11·75%). An *X*-ray crystallographic determination of the molecular weight (kindly carried out by Mr. D. Daniels) gave a value of 348 (theor. 355).

(v) *From 3-methylpiperidine.* Isatin (1·8 g.) and 3-methylpiperidine (600 mg.; b. p. 122—126°, prepared by hydrogenation of purified 3-picoline as in the previous experiment), in xylene (25 c.c.), were heated under reflux for 90 min. The blue *product* (90 mg., 3·5%) was purified and recrystallised in the usual way (Found, on a sample dried at room temperature/14 mm. for 1 hr.: C, 70·2; H, 6·0. $C_{22}H_{19}O_2N_3,CH_3{\cdot}OH$ requires C, 70·9; H, 5·95%). Longer heating of the reactants gave a brown tar.

(vi) *From* cis-*octahydroindole.* Isatin (400 mg.) and *cis*-octahydroindole [16] (200 mg.) in xylene (5 c.c.) were heated under reflux for 2 hr. The solid *product* (170 mg.) was separated and crystallised from hot methanol in the usual manner (Found, on a sample dried at 100°/0·1 mm. for 4 hr.: C, 72·1; H, 6·0; N, 10·3. $C_{24}H_{21}O_2N_3,CH_3{\cdot}OH$ requires C, 72·3; H, 6·1; N, 10·1%).

(vii) *From pyrrolidine and* N-*methylisatin.* *N*-Methylisatin (500 mg.) and pyrrolidine (500 mg.) were dissolved in 2N-acetic acid (25 c.c.) and warmed on the steam-bath for 1 hr. The solution was then heated to boiling, next cooled, and the blue solid product (465 mg., 75%) separated and washed with ethanol and ether. It was purified by slow crystallisation from methanol by the hot-extraction method, being obtained as blue glistening needles [5] (Found: N, 11·6. Calc. for $C_{22}H_{15}O_2N_3$: N, 11·9%). The infrared spectrum (in Nujol) showed no medium or strong absorption below 1673 cm.$^{-1}$. Other bands were observed at 1634, 1599, and 1582 cm.$^{-1}$.

Reaction of Isatin and iso*Indoline* (cf. Grassmann and Arnim [5]).—Isatin (1 g.) and *iso*indoline hydrochloride (500 mg.; the base was prepared by the electrolytic reduction of phthalimide according to Rollet, Dinet, and Willemart's directions [18]), in acetic acid (3·5 c.c.), were heated for 10 min. The mixture was cooled and the solid which separated (130 mg.) was removed and washed with alcohol. The spectrum of the product in solution is recorded in Table 1. In concentrated sulphuric acid the compound formed a clear blue solution.

Reaction of Acenaphthenequinone and L-*Pipecolic Acid.*—Acenaphthenequinone (300 mg.) and L-pipecolic acid (150 mg.) in ethanol (30 c.c.) were heated under reflux for 30 min. After cooling,

[17] King, King, and Thompson, *J.*, 1948, 552.
[18] Rollet, Dinet, and Willemart, *Bull. Soc. chim. France*, 1950, 877.

the greenish-brown crystalline *product* was separated, washed with ethanol, dried (179 mg.), and crystallised from methanol (Found : C, 84·0; H, 4·7; N, 3·6. $C_{29}H_{19}O_2N$ requires C, 84·2; H, 4·6; N, 3·4%).

Isatic Acid Piperidide.—Prepared from equimolecular quantities of isatin and piperidine (Liebermann and Krauss [7]), this derivative formed yellow prisms, m. p. 135° (from ethanol), and gave an *acetate*, pale yellow needles, m. p. 135° (from 50% aqueous methanol) (Found : C, 66·3; H, 6·4; N, 10·2. $C_{15}H_{18}O_3N_2$ requires C, 65·9; H, 6·6; N, 10·2%).

5-Bromoisatic Acid Piperidide.—Prepared as above from 5-bromoisatin and piperidine,[6] this piperidide formed yellow prisms, m. p. 206—208° (from ethanol), which sublimed at 140°/0·1 mm. (Found : C, 50·2; H, 5·1. Calc. for $C_{13}H_{15}O_2N_2Br$: C, 50·2; H, 4·8%), and gave a pale yellow *acetate*, m. p. 138—140° (from 50% aqueous methanol) (Found : C, 51·5; H, 4·9; N, 8·3; Br, 22·0. $C_{15}H_{17}O_3N_2Br$ requires C, 51·1; H, 4·8; N, 8·0; Br, 22·7%), and *2 : 4-dinitrophenylhydrazone*, orange-red needles, m. p. 371—373° (from nitrobenzene) (Found : N, 17·2. $C_{19}H_{19}O_5N_6Br$ requires N, 17·1%).

5-Bromoisatic Acid Morpholide.—This *derivative*, prepared as above from 5-bromoisatin and morpholine, formed yellow needles, m. p. 208—210° (decomp.) (from aqueous methanol) (Found : C, 45·7; H, 4·4; N, 8·4; Br, 23·7. $C_{12}H_{13}O_3N_2Br$ requires C, 45·6; H, 4·15; N, 8·95; Br, 25·6%). Its *acetate* formed colourless needles, m. p. 168° (from water) (Found : C, 47·1; H, 4·2. $C_{14}H_{15}O_4N_2Br$ requires C, 47·4; H, 4·2%).

5-Bromo-NN-hexamethyleneisatamide.—5-Bromoisatin (500 mg.) and hexamethyleneimine (400 mg.) were dissolved in warm methanol (2 c.c.). The solution was cooled and crystallisation of the product induced by scratching. The yellow *amide* was separated and recrystallised from methanol, to give yellow prisms (320 mg.), m. p. 165—166° (Found : C, 52·2; H, 5·3; N, 8·3. $C_{14}H_{17}N_2O_2Br$ requires C, 51·8; H, 5·25; N, 8·6%).

3 : 4-Benzisatic Acid Pyrrolidide ($CO_2H = 1$).—Prepared as above from 4 : 5-benzisatin (500 mg.) and pyrrolidine (600 mg.), the *product* (300 mg.) formed yellow prisms (from methanol), m. p. 179—180° (Found : C, 72·0; H, 6·1. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0%).

Oxidation of Isatin Blue.—(i) *With nitric acid.* Isatin blue (2 g.) was treated with concentrated nitric acid (100 c.c.; redistilled) and, when the vigorous reaction had subsided, the resulting solution was warmed for a short while and then evaporated to dryness under reduced pressure. A little water was added and the solution again evaporated to dryness, although during the evaporation a yellow steam-volatile solid (100 mg.) was obtained. The same product was the major constituent of the residue which was sublimed at 100°/0·1 mm., and yielded a further quantity (700 mg.) of the yellow solid, m. p. 118° alone and 118—119° when mixed with picric acid (Found : C, 31·4; H, 1·65. Calc. for $C_6H_3O_7N_3$: C, 31·5; H, 1·3%).

(ii) *With alkaline potassium permanganate.* Isatin blue (2 g.) was suspended in a 1% solution of potassium hydroxide (200 c.c.) at 70° and a solution of potassium permanganate (2·65 g.; theor. for oxidation of two double bonds) was added with frequent shaking during 1 hr. at 70°. The solution became green and then brownish-yellow and after the reaction had ceased the whole was filtered (Supercel) and the filtrate evaporated under reduced pressure to *ca.* 50 c.c. The residual solution was acidified with hydrochloric acid, filtered, and extracted with ether (6 × 30 c.c.) and chloroform (6 × 30 c.c.). The combined yellow ethereal extract was dried ($MgSO_4$) and the solvent removed to yield a red solid (500 mg.) which was crystallised from ethanol and was identified as isatin, m. p. and mixed m. p. 201°. A further quantity (150 mg.) was obtained from the chloroform extract. The residual aqueous layer was extracted with ether continuously for 24 hr. Evaporation of the ether gave a red gum containing some white solid. Sublimation of the residue at 60°/1 mm. gave the solid product which crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to yield oxalic acid, m. p. and mixed m. p. 97—99°.

(iii) *With excess of alkaline potassium permanganate.* The above experiment was repeated with alkaline potassium permanganate (3·33 g.). The product was treated as before and after acidification was extracted with ether (6 × 30 c.c.).

From the ethereal extract, isatin (300 mg.) was obtained. Evaporation of the aqueous solution gave a dark brown resin (1·4 g.) which was extracted with hot ethanol (2 × 50 c.c.), and the solvent removed from the extract to yield a sticky red solid which was sublimed at 76°/0·6 mm. A mixture of a yellow and a white solid sublimate (400 mg.), m. p. 95—130°, was obtained, but by repeated sublimation at 80°/0·5 mm. a compound was obtained which after crystallisation from chloroform had m. p. 140—142°. When mixed with authentic anthranilic acid it had m. p. 142—144°.

XUM

(iv) *With chromic acid.* To a suspension of isatin blue (2·2 g.) in glacial acetic acid (30 c.c.), a solution of chromic acid (1·7 g.) in acetic acid (57 c.c.) was added dropwise at room temperature during 1 hr. with shaking. The solvent was removed from the product under reduced pressure and the residue extracted repeatedly with ether. After removal of the ether from the extract isatin (350 mg.) was obtained and identified by comparison with an authentic specimen. No other recognisable products could be isolated.

Pyrolytic Degradation of Isatin Blue.—Isatin blue (700 mg.) was heated at 185°/0·1 mm. for 48 hr. Several products could be discerned in the sublimate but the most volatile product was easily separated from the others. This was repeatedly sublimed at 72°/0·1 mm., being obtained as a pale yellow crystalline compound (8·5 mg.), m. p. 125° (Found: C, 71·7; H, 5·1. Calc. for C_8H_7ON: C, 72·15; H, 5·3%). When mixed with authentic oxindole, it had m. p. 125—127°.

We are grateful to the directors of the Metal Box Co., Ltd., for granting leave of absence to one of us (D. J. McC.) in order to carry out this work.

THE UNIVERSITY, NOTTINGHAM. [*Received, March 19th*, 1957.]

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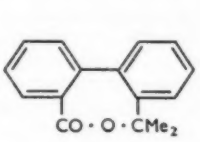
692. *The Isomerisation of the Lactone of* 2′-(1-*Hydroxy*-1-*methylethyl*)-*diphenyl*-2-*carboxylic Acid.*

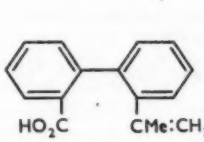
By PAULINE M. EVERITT and E. E. TURNER.

When the lactone (I) is heated with anhydrous formic acid or with 50% sulphuric acid, 9 : 9-dimethylfluorene-4-carboxylic acid (III) is produced. When the lactone (I) is heated with alumina, 2′-(1-methylvinyl)diphenyl-2-carboxylic acid (II) is obtained.

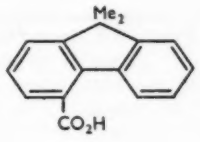
IN an attempt to obtain 2′-(1-methylvinyl)diphenyl-2-carboxylic acid (II) by heating the lactone (I) with anhydrous formic acid or with 50% sulphuric acid, 9 : 9-dimethylfluorene-4-carboxylic acid (III) was isolated. This led us to find that 9 : 9-dialkylfluorenes had been obtained from dialkyl-2-diphenylylcarbinols, and 9 : 9-diphenylfluorene-4-carboxylic



(I)



(II)



(III)

acid from 2′-(α-hydroxydiphenylmethyl)diphenyl-2-carboxylic acid [1] in presence of acids. Decarboxylation of the acid (III) gave 9 : 9-dimethylfluorene, whilst treatment of its methyl ester with methylmagnesium iodide gave 4-(1-hydroxy-1-methylethyl)-9 : 9-dimethylfluorene, from which by dehydration, followed by hydrogenation, 9 : 9-dimethyl-4-*iso*propylfluorene was obtained.

The desired 2′-(1-methylvinyl)diphenyl-2-carboxylic acid (II) was later obtained by heating the lactone (I) with alumina. It was hydrogenated to 2′-*iso*propyldiphenyl-2-carboxylic acid, identical with the product of fusing 9 : 10-dihydro-9 : 9-dimethyl-10-oxophenanthrene with potassium hydroxide.[2] Decarboxylation of the *iso*propyl acid gave 2-*iso*propyldiphenyl [$\lambda_{max.}$ 233 mμ (ε 8800), $\lambda_{min.}$ 225 mμ (ε 8100) in 95% EtOH; cf. ref. 3].

[1] Anchel and Blatt, *J. Amer. Chem. Soc.*, 1941, **63**, 1948; Sergeev, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 1421.
[2] Meerwein, *Annalen*, 1913, **396**, 225.
[3] Braude and Forbes, *J.*, 1955, 3776; A.P.I. Research Project No. 44, no. 285.

XUM

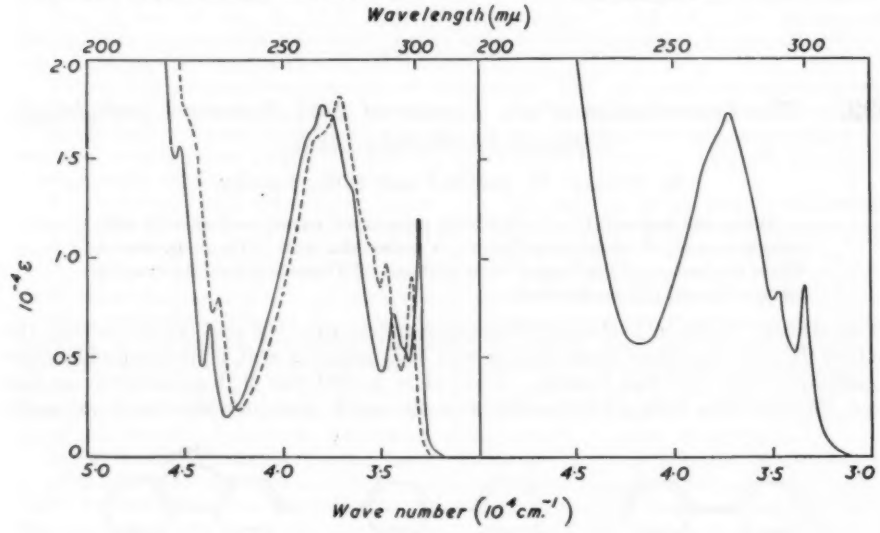
The ultraviolet absorption spectra (Figs. 1 and 2; Table) of the 9 : 9-dimethylfluorenes suggest that the steric effect of a substituent such as *iso*propyl in the 4-position is much

	Diphenyl band		Long-wave band	
Compound (in 95% EtOH)	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
9 : 9-Dimethylfluorene	263	17,500	290, 302	7100, 12,000
9 : 9-Dimethyl-4-*iso*propylfluorene	269	18,000	287·5, 298·5	9600, 9000
9 : 9-Dimethyl-4-(1-methylvinyl)fluorene ...	268·5	17,000	288, 299·5	8200, 8500

less than in the corresponding position in diphenyl; presumably this is due to the planar, non-collinear configuration of fluorene [4] which leaves more space for an *ortho*-substituent.

FIG. 1. *Absorption of* (——) 9 : 9-*dimethylfluorene and* (– – – –) 9 : 9-*dimethyl*-4-iso*propylfluorene.*

FIG. 2. *Absorption of* 9 : 9-*dimethyl*-4-(1-*methylvinyl*)*fluorene.*



EXPERIMENTAL

9 : 9-*Dimethylfluorene*-4-*carboxylic Acid.*—(*a*) A solution of 2′-(1-hydroxy-1-methylethyl)diphenyl-2-carboxylic lactone (1 g.) in anhydrous formic acid (20 c.c.) was boiled under reflux for 4 hr. The cooled solution deposited crystals which were filtered off, dissolved in ether, washed with brine, and then extracted with 30% aqueous sodium hydroxide. The alkaline extract was acidified and the precipitate filtered off and dried (0·6 g.). After crystallisation from benzene the dimethylfluorenecarboxylic acid (0·4 g.) had m. p. 195—196°.

(*b*) A mixture of the lactone (25 g.) and 50% sulphuric acid (250 c.c.) was boiled under reflux for 1 hr., then cooled and poured into ice-water. Extraction with ether, etc., as in (*a*), gave 20 g. of dimethylfluorenecarboxylic acid.

Methyl 9 : 9-*dimethylfluorene*-4-*carboxylate*, obtained from the acid by treatment with thionyl chloride and then methanol, formed hexagonal prisms, m. p. 82—83°, from methanol (Found : C, 80·9; H, 6·4. $C_{17}H_{16}O_2$ requires C, 80·95; H, 6·4%). The *amide*, prepared from the acid by the successive use of thionyl chloride and aqueous ammonia, had m. p. 180·5—181·5° after crystallisation from aqueous ethanol (Found : N, 5·8. $C_{16}H_{15}ON$ requires N, 5·9%).

[4] Brown and Bortner, *Acta Cryst.*, 1954, **7**, 139; Burns and Iball, *Nature*, 1954, **173**, 635.

9 : 9-*Dimethylfluorene*.—A solution of the fluorene-acid (2 g.) in quinoline (20 c.c.), containing a little copper bronze in suspension, was boiled for 3 hr. and then poured into dilute hydrochloric acid. The solution was extracted with ether, and the ethereal solution suitably washed. Evaporation, followed by crystallisation from aqueous ethanol (charcoal), gave the dimethylfluorene (1·1 g.), m. p. 95—96° (Found : C, 92·7; H, 7·3. Calc. for $C_{15}H_{14}$: C, 92·8; H, 7·2%).

4-(1-*Hydroxy*-1-*methylethyl*)-9 : 9-*dimethylfluorene*.—Methyl 9 : 9-dimethylfluorene-4-carboxylate (11·5 g., 1·0 mol.) was added to a Grignard reagent prepared from 5 g. (4·5 atom-equiv.) of magnesium and methyl iodide. The mixture was boiled for 5 hr., cooled, decomposed, and worked up in the usual way. The *hydroxy-compound* (6 g., 52%) crystallised from dilute ethanol in prisms, m. p. 118—119° after vacuum-drying (Found : C, 85·2; H, 8·1. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%).

9 : 9-*Dimethyl*-4-(1-*methylvinyl*)*fluorene*.—A mixture of the above hydroxy-compound (3 g.) and 50% sulphuric acid (75 c.c.) was boiled under reflux for 2 hr. and then poured into ice-water. Extraction with ether and normal working up gave the *hydrocarbon* (2·1 g., 75%) which crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 67—68° (Found : C, 92·4; H, 7·7. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%).

9 : 9-*Dimethyl*-4-iso*propylfluorene*.—A solution of the 1-methylvinylfluorene (1·5 g.) in ethanol (50 c.c.) and platinum oxide (0·5 g.) was shaken in hydrogen (95 lb./sq. in.) for 5 hr. After normal procedure the *hydrocarbon* crystallised from dilute ethanol (charcoal) as plates, m. p. 48—49° (1·2 g.) (Found : C, 91·4; H, 8·7. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%).

2′-iso*Propyldiphenyl*-2-*carboxylic Acid*.—It was found advantageous to carry out the fusion of 9 : 10-dihydro-9 : 9-dimethyl-10-oxophenanthrene with less potassium hydroxide than Meerwein [5] used and at 185—190° instead of at 220—240°. The yield was 61% and the m. p. 110—111° (Meerwein gave m. p. 104—106°) (Found : C, 80·4; H, 6·9. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%).

The *amide*, prepared *via* the acid chloride, after being crystallised from light petroleum (b. p. 100—120°) had m. p. 115·5—116·5° (Found : N, 5·8. $C_{16}H_{17}ON$ requires N, 5·9%).

2-iso*Propyldiphenyl*.—A solution of the preceding carboxylic acid (2·4 g.) in quinoline (15 c.c.) containing a little copper bronze was boiled for 4 hr., then cooled and poured into dilute hydrochloric acid. Extraction with ether, followed by removal of the ether and distillation over sodium, gave 2-*iso*propyldiphenyl, needles m. p. 25—26° (from ethanol). Goodman and Wise [5] found m. p. 24·46°.

Isomerisation of 2′-(1-*Hydroxy*-1-*methylethyl*)*diphenyl*-2-*carboxylic Lactone*.—A mixture of the lactone (3 g.) and alumina (1 g.) was heated from 150° to 260° during 20 min. After cooling, the product was extracted with ether and the extract washed and extracted with alkali. Acidification of the alkaline extracts gave 2′-(1-*methylvinyl*)*diphenyl*-2-*carboxylic acid*, which after crystallisation from dilute ethanol and then light petroleum (b. p. 100—120°) formed prisms, m. p. 122° (Found : C, 80·6; H, 5·4. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%).

Reduction of 2′-(1-*Methylvinyl*)*diphenyl*-2-*carboxylic Acid*.—The unsaturated acid (0·5 g.) in ethanol (20 c.c.) with platinum oxide catalyst (0·05 g.) was shaken in hydrogen for 6 hr. at 95 lb./sq. in. Normal working up, followed by crystallisation from dilute ethanol, gave 2′-*iso*propyldiphenyl-2-carboxylic acid, m. p. and mixed m. p. with above acid 110—111°.

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Bedford College, University of London. [*Received, April 9th*, 1957.]

[5] Goodman and Wise, *J. Amer. Chem. Soc.*, 1950, **72**, 3076.

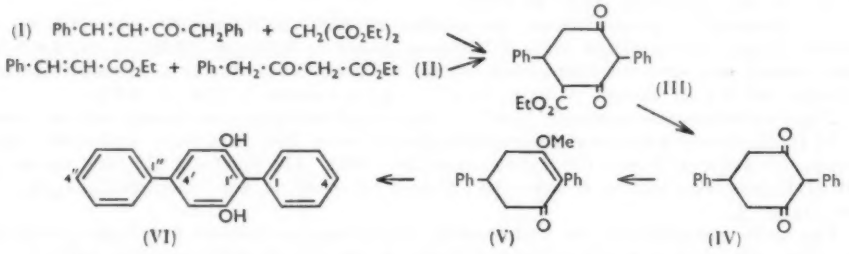
XUM

693. cyclo*Hexane*-1 : 3-*diones. Part II.* A New Synthesis of Substituted* p-*Terphenyls.*

By G. R. Ames and W. Davey.

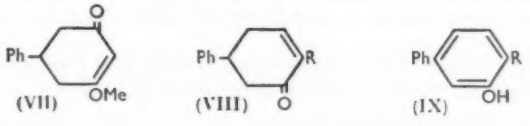
A new synthesis of *p*-terphenyls substituted in the central ring is described. 2 : 5-Diphenyl*cyclo*hexane-1 : 3-dione, which is readily accessible by Michael addition of diethyl malonate to benzyl styryl ketone, is converted into 2′-hydroxy-, 2′-cyano-, 2′-amino-, and 2′ : 6′-dihydroxy-*p*-terphenyl and *p*-terphenyl-2′-carboxylic acid.

A route to 2′ : 6′-dihydroxy-*p*-terphenyl (VI) and other unsymmetrical terphenyls has been developed by an extension of Suter and Smith's synthesis [1] of 3 : 5-dihydroxydiphenyl from benzylideneacetone *via* 5-phenyl*cyclo*hexane-1 : 3-dione.



The dione-ester (III) was prepared in 79% yield by the ethoxide-catalysed addition of diethyl malonate to benzyl styryl ketone [2] (I), or, less conveniently, by Michael addition of ethyl γ-phenylacetoacetate (II) to ethyl cinnamate (ethyl γ-phenylacetoacetate was conveniently prepared by Bowman's general method for β-keto-esters [3] from phenylacetyl chloride and diethyl ethoxymagnesiomalonate). Alkaline hydrolysis of the dione-ester (III) yielded the dione (IV), which was converted by diazomethane into the enol ether (V). Dehydrogenation of the latter by sulphur, followed by demethylation, gave the required 2′ : 6′-dihydroxy-*p*-terphenyl (VI) in 35% overall yield from the ketone (I).

As a model for the preparation of 2′-hydroxy-*p*-terphenyl (IX; R = Ph), obtained by Fichter and Grether [4] by another route, 5-phenyl*cyclo*hexane-1 : 3-dione was converted by diazomethane into the enol ether (VII), which was reduced by lithium aluminium hydride to the unsaturated ketone (VIII; R = H), dehydrogenation of which by sulphur afforded the



known 3-hydroxydiphenyl (IX; R = H). The enol ether (V) was then reduced with a slight excess of lithium aluminium hydride and dehydrogenated with sulphur, 2′-hydroxy-*p*-terphenyl (45%) and *p*-terphenyl (23%) being obtained. The *p*-terphenyl presumably arises because in the preparation of the ketone (VIII; R = Ph), some over-reduction occurs, giving an alcohol, which is dehydrated and dehydrogenated when heated with sulphur.

* Part I, *J.*, 1956, 3001.

[1] Suter and Smith, *J. Amer. Chem. Soc.*, 1939, **61**, 166.
[2] Goldschmiedt *et al.*, *Monatsh.*, 1897, **18**, 437; 1898, **19**, 461; 1901, **22**, 659.
[3] Bowman, *J.*, 1950, 322.
[4] Fichter and Grether, *Ber.*, 1903, **36** 1407.

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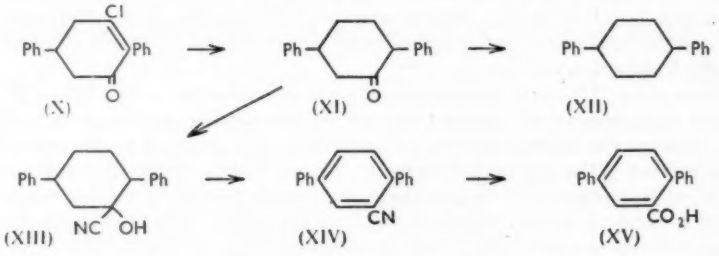
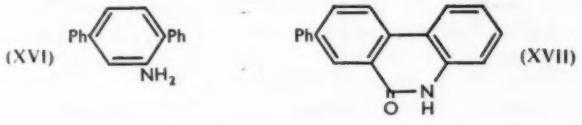
An attempt to prepare 2 : 5-diphenyl*cyclo*hexanone (XI), by palladium-catalysed hydrogenation of the crude ketone (VIII; R = Ph), failed, the only crystalline product being an isomer of 2 : 5-diphenyl*cyclo*hexanol.

Treatment of the dione (IV) with phosphorus trichloride in boiling chloroform afforded the chloro-ketone (X), which was not isolated but was hydrogenated, at a palladium catalyst, to 2 : 5-diphenyl*cyclo*hexanone (XI), of which only one isomer could be isolated. Wolff–Kishner reduction converted this into 1 : 4-diphenyl*cyclo*hexane (XII). Our product corresponds to the isomer obtained by Nenitzescu and Curcăneanu [5] and by Sidorova, Feiershtein, and Kochetkova [6] as one of the products from the aluminium chloride-catalysed reaction of benzene with 1 : 2-dichloro*cyclo*hexane and 2-phenyl*cyclo*hexanol respectively, and known [5, 6] to give *p*-terphenyl on dehydrogenation with selenium.



The cyanohydrin (XIII), obtained by the very convenient exchange reaction described by Nazarov, Akhrem, and Kamernitsky,[7] when treated with acetic anhydride and then dehydrogenated with selenium, gave 2′-cyano-*p*-terphenyl (XIV) (43%) and 4% of *p*-terphenyl (presumably some elimination of hydrogen cyanide occurred during dehydrogenation). Hydrolysis of the nitrile (XIV) furnished *p*-terphenyl-2′-carboxylic acid (XV).

Preparation of 2′-amino-*p*-terphenyl (XVI) from the dione (IV) proved difficult. The amine has been synthesised by Basford [8] by nitration of 4-*cyclo*hexyldiphenyl to 4-*cyclo*hexyl-2-nitrodiphenyl, dehydrogenation to 2′-nitro-*p*-terphenyl, and reduction of the latter. Horning and Horning [9] found that substituted anilines could be prepared by palladium-catalysed dehydrogenation of *cyclo*hexenone azines; however, the amine (XVI) was not



obtained on attempted dehydrogenation of the azine of the ketone (VIII; R = Ph) or that of (XI). Attempts to dehydrogenate the benzylamine condensation product of the *cyclo*hexenone (VIII; R = Ph) and the phenylhydrazone of the *cyclo*hexanone (XI) by sulphur also failed. No crystalline product was obtained on attempted Wolff aromatisation [10] of the oxime of the ketone (VIII; R = Ph). In the Schmidt reaction the acid (XV) gave an unrecognisable sulphur-containing product, and the amide of the acid (XV) did not undergo the Hofmann reaction (a similar result was reported by Bradsher and Sverlick [11] for

[5] Nenitzescu and Curcăneanu, *Ber.*, 1937, **70**, 346.
[6] Sidorova, Feiershtein, and Kochetkova, *J. Gen. Chem.* (*U.S.S.R.*), 1956, **26**, 201 (U.S. translation).
[7] Nazarov, Akhrem, and Kamernitsky, *ibid.*, 1955, **25**, 1291 (U.S. translation).
[8] Basford, *J.*, 1937, 1440.
[9] Horning and Horning, *J. Amer. Chem. Soc.*, 1947, **69**, 1907.
[10] Horning, *Chem. Rev.*, 1943, **33**, 89.
[11] Bradsher and Sverlick, *J. Amer. Chem. Soc.*, 1950, **72**, 4189.

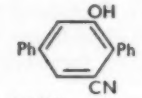
XUM

m-terphenyl-4-carboxyamide). Finally, Curtius degradation of *p*-terphenyl-2′-carboxylic acid (XV), in the conditions successfully used for *m*-terphenyl-4-carboxylic acid by Bradsher and Sverlick,[11] gave a 28% yield of 2′-amino-*p*-terphenyl, with a by-product (8%) which was probably 7-phenylphenanthridone (XVII).

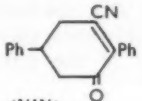
In an attempt to prepare 2′-cyano-6′-hydroxy-*p*-terphenyl (XVIII), the enol ether (V) was subjected to the acetone cyanohydrin exchange reaction. A 93% yield of a compound $C_{19}H_{15}ON$ was obtained, whose infrared spectrum showed bands at 2215, 1691, and 1607 cm.$^{-1}$, which are attributed to conjugated nitrile,[12] αβ-unsaturated ketone,[13] and phenyl [14] systems. This compound is therefore assigned structure (XIX), being formed by displacement of the methoxy- by the cyano-group. It did not give pure compounds when heated with sulphur.

The cyano-ketone (XIX) was reduced by potassium borohydride to 3-cyano-2 : 5-diphenyl*cyclo*hex-2-en-1-ol (XX). Dehydrogenation of the latter gave *p*-terphenyl (7%) as the only crystalline product; presumably some elimination of hydrogen cyanide occurred during dehydrogenation (cf. above).

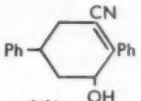
The dione-ester (III) with diazomethane gave an enol-ether, m. p. 137—138°, in 28% yield. The remainder of the product was an oil, presumably an isomer or a mixture of isomers. Neither the crystals nor the oil could be dehydrogenated to the acid (XXI) or a derivative thereof. The oily enol ether gave a 2% yield of the dione (IV), together with an oil, which, on hydrolysis with hydrochloric acid, gave 2′ : 6′-dihydroxy-*p*-terphenyl (VI) (11%) and 5-oxo-3 : 6-diphenylhexanoic acid (XXII) (4%), which was also obtained by hydrolysis of the dione-ester (III). Dehydrogenation of the crystalline enol ether also gave the dione (IV) (5%), as well as an oil which with dimethyl sulphate yielded a further 3% of the dione (IV) and an 11% yield of 2′ : 6′-dimethoxy-*p*-terphenyl (XXIII) (see below).



(XVIII)

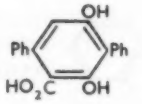


(XIX)

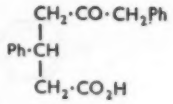


(XX)

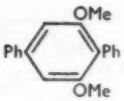
A number of new compounds have been prepared from the hydroxyterphenyls (VI) and (IX; R = Ph). The latter was converted by diazomethane into 2′-methoxy-*p*-terphenyl (XXIV; R = H); an attempt to prepare the aldehyde (XXIV; R = CHO) by treatment



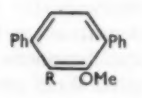
(XXI)



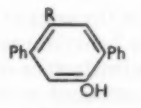
(XXII)



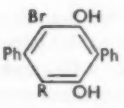
(XXIII)



(XXIV)



(XXV)



(XXVI)

with phosphorus oxychloride–dimethylformamide was unsuccessful. With benzenediazonium chloride it gave an azo-compound, probably (XXV; R = Ph·N:N), which was reduced by zinc in acetic acid–acetic anhydride to the acetamido-compound (XXV; R = NHAc).

[12] Kitson and Griffith, *Analyt. Chem.*, 1952, **24**, 334.
[13] Cromwell, Miller, Johnson, Frank, and Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337.
[14] Barnes, Gore, Stafford, and Williams, *Analyt. Chem.*, 1948, **20**, 402.

In contrast to 2'-hydroxy-*p*-terphenyl, 2' : 6'-dihydroxy-*p*-terphenyl (VI) reacts abnormally with diazomethane. The product, m. p. 135—136°, obtained in 64% yield, had the empirical formula $C_{21}H_{21}O_3N$. No titratable groups could be detected on potentiometric titration, and the infrared spectrum contained a band (1704 cm.$^{-1}$) due to a carbonyl group. The compound therefore appears to contain an amide group.

2' : 6'-Dimethoxy-*p*-terphenyl (XXIII) was obtained quantitatively by means of dimethyl sulphate. Attempts to prepare a terphenyl aldehyde by the Gattermann reaction on 2' : 6'-dihydroxy-*p*-terphenyl (VI) and by treatment of 2' : 6'-dimethoxy-*p*-terphenyl (XXIII) with phosphorus oxychloride–dimethyl formamide were unsuccessful. The resorcinol (VI) with bromine gave the monobromo-compound (XXVI; R = H), which was further brominated to the dibromo-compound (XXVI; R = Br).

The ultraviolet absorption spectra of many of the above compounds are recorded in

Ultraviolet absorption spectra in ethanol (italicised numerals denote an inflexion).

Compound	$\lambda_{max.}$ (mμ)	ε	Compound	$\lambda_{max.}$ (mμ)	ε	Compound	$\lambda_{max.}$ (mμ)	ε
(a) *Terphenyls*								
p-Terphenyl [a]	278	32,700	(VI)	*225*	33,100	(XXVI; R = Br)	*228*	26,700
(IX; R = Ph)	271·5	24,700		272	24,600		*252*	13,000
(XXIV; R = H)	270	24,500	(XXIII)	*225*	28,500		296	3,160
(XIV)	*229*	25,500		272	20,600	(XXV; R =	237	23,100
	272	24,700	(XXVI; R = H)	258	15,700	Ph–N=N)	*245*—	23,000
(XV)	*234*	17,700	(XXV; R =	*232*	23,900		*520*	
	268	24,000	NHAc)	*260*	19,000		287	22,800
				304	7,400		367	19,100
(b) *Other compounds*								
(III)	*230*	11,800	(VIII; R = H)	224	11,000	(XI)	*242*	225
	270	11,500	(VIII; R = Ph)	259	5,700		*247*	300
Enol ether of (III)	273·5	13,500	(XIX)	234	12,600		252	405
(IV)	*230*	10,000		292	5,060		258	489
	268	12,000	(XVII)	260	32,600		264	380
(V)	*224*—	13,000					*267*	266
	228						288	94
	271	13,000						

[a] Gillam and Hey (*J.*, 1939, 1170) report $\lambda_{max.}$ 276 mμ (ε 35,000) in hexane and 280 mμ (ε 25,000) in chloroform.

the Table. The spectra of the 2'-substituted terphenyls show a slight hypsochromic shift (6—10 mμ) with respect to *p*-terphenyl; there is also a lowering of the molecular extinction coefficient. Similar results have been recorded for 2-substituted diphenyls.[15] Introduction of a further group in the 6'-position does not cause a further hypsochromic shift. However, when substitution of bromine occurs at the 3'- and 5'-positions of 2' : 6'-dihydroxy-*p*-terphenyl (VI), there is a marked lowering of the intensity of absorption, presumably because of steric hindrance to coplanarity of the terminal phenyl rings.

The spectra of the dione-ester (III) and dione (IV) are very similar to those of the corresponding enol ethers, which indicates that both compounds are fully enolised.

Experimental

Ultraviolet absorption spectra were determined in 96% ethanol, with a Unicam S.P. 500 Spectrophotometer. " Light petroleum " refers to the fraction, b. p. 60—80°.

Ethyl γ-Phenylacetoacetate (II).—To a benzene solution of diethyl ethoxymagnesiomalonate [3] (from magnesium, 46 g., and diethyl malonate, 320 g.) was added, during 1 hr., phenylacetyl chloride (from the acid, 136 g., and thionyl chloride). The mixture was stirred under reflux for 3 hr., then cooled and poured into ice-cold dilute sulphuric acid. The organic layer was separated, washed thoroughly with water, dried ($MgSO_4$) and evaporated. The crude acylmalonate was refluxed with acetic acid (300 c.c.) containing sulphuric acid (1·3 g.) for 3 hr

[15] *E.g.*, Braude and Forbes, *J.*, 1955, 3776.

Barium carbonate (6 g.) was then added, and the solution filtered and evaporated. Fractionation *in vacuo* yielded 1-phenylpropan-2-one (40 g., 30%), b. p. 59—62°/1·6 mm., and ethyl γ-phenylacetoacetate (86·1 g., 43%), b. p. 119—121°/1·5 mm. (lit., b. p. 100—101°/14 mm. and 153—155°/9 mm. respectively).

Ethyl 2 : 4-*Dioxo*-3 : 6-*diphenyl*cyclo*hexanecarboxylate* (III).—(a) *From* 1 : 4-*diphenylbut*-1-*en*-3-*one and diethyl malonate.* To sodium (2·65 g.), dissolved in dry ethanol (50 c.c.), was added diethyl malonate (18·2 g.), followed by 1 : 4-diphenylbut-1-en-3-one [2] (25·2 g.) in ethanol (200 c.c.), and the mixture set aside overnight. The solution was concentrated, diluted with water, and filtered. Acidification of the filtrate afforded 30·2 g. (79%) of material, m. p. 157—164°. *Ethyl* 2 : 4-*dioxo*-3 : 6-*diphenyl*cyclo*hexanecarboxylate* formed needles, m. p. 174—175°, from benzene (Found : C, 74·8; H, 5·9. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0%).

(b) *From ethyl γ-phenylacetoacetate and ethyl cinnamate.* A series of experiments was conducted to find the optimum conditions. Ethyl γ-phenylacetoacetate and ethyl cinnamate were successively added to sodium ethoxide in ethanol, and the mixture refluxed for 6 hr., then poured into water. Any unchanged reactants were removed by ether; acidification of the aqueous layer afforded the dione-ester. Best results (43% yield) were obtained with ethyl γ-phenylacetoacetate (1 mol.), ethyl cinnamate (4 mols.), and sodium ethoxide (1 mol.).

2 : 5-*Diphenyl*cyclo*hexane*-1 : 3-*dione* (IV).—Ethyl 2 : 4-dioxo-3 : 6-diphenyl*cyclo*hexanecarboxylate (30 g.) was refluxed for 10 hr. with sodium carbonate (decahydrate; 60 g.) in water (180 c.c.). The solution was acidified and then brought to the boil. The *dione* formed square plates, m. p. (inserted at 220°) 247—249°, from 2-methoxyethanol (Found : C, 81·2; H, 6·1. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

3-*Methoxy*-2 : 5-*diphenyl*cyclo*hex*-2-*en*-1-*one* (V).—The preceding compound, in methanol, treated with ethereal diazomethane, gave the *enol ether*, prisms, m. p. 137—138°, from light petroleum (Found : C, 82·0; H, 6·5. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

2′ : 6′-*Dihydroxy*-p-*terphenyl* (VI).—The foregoing enol ether (2·5 g.) was heated at 270° for 2 hr. with sulphur (0·3 g.). The cooled product was taken up in chloroform, and some 2 : 5-diphenyl*cyclo*hexane-1 : 3-dione (0·3 g.) removed by washing with aqueous sodium carbonate. The chloroform was evaporated and the residue refluxed with 58% hydriodic acid (3 c.c.) and acetic acid (8 c.c.) for 15 hr. Water (50 c.c.) was added and the mixture made just acid to Congo-red. 2′ : 6′-*Dihydroxy*-p-*terphenyl* (1·6 g.) crystallised from benzene as prisms, m. p. 206—207° (Found : C, 82·3; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). The enol ether was recovered unchanged on attempted dehydrogenation by palladised charcoal in refluxing *p*-cymene.

3-*Methoxy*-5-*phenyl*cyclo*hex*-2-*en*-1-*one* (VII).—5-Phenyl*cyclo*hexane-1 : 3-dione [16] (16 g.) in methanol was treated with ethereal diazomethane in the usual way. The *enol ether* (15·3 g.), which had b. p. 146—147°/0·6 mm., n_D^{20} 1·5767, crystallised (m. p. 32—34°) (Found : C, 76·7; H, 7·0. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%).

5-*Phenyl*cyclo*hex*-2-*en*-1-*one* (VIII; R = H).—The above enol ether (5 g.) in ether (100 c.c.) was slowly added to lithium aluminium hydride (1·2 g.) in ether (100 c.c.), and the mixture refluxed for 1 hr. Working up in the usual way gave 5-*phenyl*cyclo*hex*-2-*en*-1-*one*, b. p. 115—116°/1 mm., n_D^{19} 1·5693 (Found : C, 84·2; H, 7·4. $C_{12}H_{12}O$ requires C, 83·7; H, 7·0%).

3-*Hydroxydiphenyl* (IX; R = H).—5-Phenyl*cyclo*hex-2-en-1-one (2·3 g.) was heated at 260—270° for 1 hr. with sulphur (0·44 g.). Isolation of the acidic fraction yielded an oil, which on extraction with boiling light petroleum, yielded 3-hydroxydiphenyl, blades, m. p. 74—75°. Jacobsen and Loeb [17] record m. p. 75°, and Errara and La Spada [18] 78°.

2 : 5-*Diphenyl*cyclo*hex*-2-*en*-1-*one* (VIII; R = Ph).—3-Methoxy-2 : 5-diphenyl*cyclo*hex-2-en-1-one (5·3 g.) in benzene (100 c.c.) was added to lithium aluminium hydride in ether (75 c.c. of a 1% solution), and the mixture refluxed for 1 hr. Working up in the usual way yielded 2 : 5-*diphenyl*cyclo*hex*-2-*en*-1-*one* (3·8 g.), needles, m. p. 110—111° (from methanol) (Found : C, 87·2; H, 6·4. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%). The *oxime* crystallised from ethanol as needles, m. p. 206—207° (Found : C, 81·9; H, 6·5; N, 5·2. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5; N, 5·3%).

Dehydrogenation of 2 : 5-*Diphenyl*cyclo*hex*-2-*en*-1-*one.*—The crude ketone (from 5·3 g. of enol ether) was heated with sulphur (0·72 g.) at 240°, the temperature being slowly raised to 300°.

[16] Vorländer, *Ber.*, 1894, **27**, 2053.
[17] Jacobsen and Loeb, *ibid.*, 1903, **36**, 4082.
[18] Errara and La Spada, *Gazzetta*, 1905, **35**, II, 539.

Recrystallisation from ethyl methyl ketone gave *p*-terphenyl (1 g.), plates, m. p. 213—214° (lit., 213°) (Found : C, 93·8; H, 6·2. Calc. for $C_{18}H_{14}$: C, 93·9; H, 6·1%). Evaporation of the mother-liquors yielded 2′-hydroxy-*p*-terphenyl (IX; R = Ph) (2·1 g.), needles, m. p. 192—193° (from benzene) (Fichter and Grether [4] report m. p. 194°).

2′-Hydroxy-*p*-terphenyl with diazomethane afforded *2′-methoxy*-p-*terphenyl*, prisms, m. p. 97—98°, from methanol (Found : C, 88·0; H, 6·1. $C_{19}H_{16}O$ requires C, 87·7; H, 6·2%).

2 : 5-*Diphenyl*cyclo*hexanol*.—2 : 5-Diphenyl*cyclo*hex-2-en-1-one (crude; 5 g.) in ethanol (100 c.c.) was shaken under hydrogen in the presence of 5% palladised charcoal (1 g.), until absorption ceased. The catalyst was removed and the solution evaporated. The only crystalline solid isolable was 2 : 5-*diphenyl*cyclo*hexanol* (1·4 g.), needles, m. p. 185—186°, from benzene (Found : C, 86·0; H, 7·9. $C_{18}H_{20}O$ requires C, 85·7; H, 8·0%). The compound showed no infrared absorption in the carbonyl region.

2 : 5-*Diphenyl*cyclo*hexanone* (XI).—2 : 5-Diphenyl*cyclo*hexane-1 : 3-dione (18·4 g.) in chloroform (50 c.c.) was refluxed with phosphorus trichloride (5·2 c.c.) for 3 hr. Crushed ice, ether, and aqueous sodium hydrogen carbonate were successively added, and the organic layer was separated, washed with aqueous sodium hydroxide, dried ($MgSO_4$), and evaporated. The crude chloro-ketone (10·6 g.) was shaken in ethanol (250 c.c.) under hydrogen with palladous chloride (0·2 g.) and triethylamine (20 c.c.). When the filtered solution was concentrated, there separated 2 : 5-*diphenyl*cyclo*hexanone* (5·8 g.), plates, m. p. 154—155° (from ethanol) (Found : C, 86·1; H, 7·2. $C_{18}H_{18}O$ requires C, 86·4; H, 7·2%). The *oxime* crystallised from ethyl acetate as plates, m. p. 231° (decomp.) (Found : C, 81·1; H, 6·9; N, 5·3. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

The *azine*, prepared from the ketone (1 g.) in ethanol (30 c.c.) and 1·7 c.c. of a solution of hydrazine hydrate (78%; 22·9 g.) and concentrated hydrochloric acid (3 drops) in ethanol (made up to 250 c.c.), under reflux for 1 hr., formed needles, m. p. 177—178°, from ethyl acetate (Found : C, 86·9; H, 7·8; N, 5·1. $C_{36}H_{36}N_2$ requires C, 87·1; H, 7·3; N, 5·6%).

1 : 4-*Diphenyl*cyclo*hexane* (XII).—2 : 5-Diphenyl*cyclo*hexanone (2·8 g.), ethylene glycol (50 c.c.), 78% hydrazine hydrate (5 c.c.), and potassium hydroxide (1·8 g.) in water (4 c.c.) were refluxed together for 6 hr., the internal temperature being allowed to rise to 200° after 1·5 hr. 1 : 4-Diphenyl*cyclo*hexane (1·6 g.), which separated on cooling, was collected : it crystallised from ethanol in plates, m. p. 171—172° (Found : C, 91·4; H, 8·6. Calc. for $C_{18}H_{20}$: C, 91·5; H, 8·5%). Nenitzescu and Curcăneanu [5] record m. p. 172°; Sidorova, Feiershtein, and Kochetkova [6] give m. p. 168°.

p-*Terphenyl*.—1 : 4-Diphenyl*cyclo*hexane (2 g.) was heated for 2 hr. at 350° with selenium (4 g.). The cooled product was dissolved in hot ethanol (400 c.c.), and selenium removed by filtration. The cooled filtrate deposited 1·6 g. of *p*-terphenyl, m. p. 212—213° (lit., 213°) (Found : C, 93·7; H, 6·2. Calc. for $C_{18}H_{14}$: C, 93·9; H, 6·1%).

2 : 5-*Diphenyl*cyclo*hexanone Cyanohydrin* (XIII).—To the ketone (1 g.), dissolved in acetone cyanohydrin (30 c.c.), was added saturated methanolic potassium hydroxide (0·2 c.c.), and the mixture was set aside overnight. Pouring it into water then yielded the *cyanohydrin* (1·05 g.), which crystallised from light petroleum as needles, m. p. 134—135° (Found : C, 82·3; H, 7·0; N, 5·0. $C_{19}H_{19}ON$ requires C, 82·3; H, 6·9; N, 5·1%).

2′-Cyano-p-terphenyl (XIV).—The foregoing cyanohydrin (2 g.) was refluxed for 1 hr. with acetic anhydride (20 c.c.) containing one drop of sulphuric acid. The mixture was poured into water (500 c.c.) and left overnight. The crude acetyl derivative thus obtained was heated at 350° for 2 hr. with selenium (2 g.). Fractional crystallisation from ethanol gave *p*-terphenyl (0·07 g.), m. p. and mixed m. p. 212—213°, and *2′-cyano*-p-*terphenyl* (0·7 g.), prisms, m. p. 106—107° (Found : C, 89·8; H, 5·1; N, 5·1. $C_{19}H_{13}N$ requires C, 89·4; H, 5·1; N, 5·5%).

p-*Terphenyl-2′-carboxylic Acid* (XV).—(i) A mixture of 2′-cyano-*p*-terphenyl (2·8 g.), ethylene glycol (50 c.c.), and potassium hydroxide (1·8 g.) in water (2 c.c.) was heated to remove the water and then refluxed for 20 hr. The cooled mixture was poured into water (200 c.c.) and ethyl acetate (100 c.c.), and the acidic fraction extracted with 2N-potassium hydroxide. On acidification, the potassium salt of the acid was obtained. The latter was dissolved in boiling 50% aqueous acetic acid (300 c.c.), and dilute sulphuric acid (20 c.c.) added. On cooling, there separated p-*terphenyl-2′-carboxylic acid* (1·3 g.), rods, m. p. 178—179° (from benzene) (Found : C, 83·3; H, 5·2. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%).

The *amide*, prepared *via* the acid chloride, formed needles, m. p. 193—194°, from benzene (Found : C, 84·0; H, 5·6. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5%).

XUM

(ii) 2 : 5-Diphenyl*cyclo*hexanone cyanohydrin (5 g.) was refluxed for 30 min. with pyridine (10 c.c.), phosphorus oxychloride (5 c.c.), and benzene (50 c.c.). The mixture was poured on ice and extracted with ethyl acetate : the organic layer was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated. The material thus obtained was heated at 350° for 2 hr. with selenium (5 g.), cooled, and extracted with ethanol (Soxhlet). Concentration of the extracts gave *p*-terphenyl (0·6 g.) and an oil. The latter was hydrolysed by potassium hydroxide in ethylene glycol as described in (i). Isolation of the acidic fraction afforded *p*-terphenyl-2′-carboxylic acid (0·35 g.), identical with that obtained previously.

Curtius Degradation of p-*Terphenyl-2′-carboxylic Acid.*—The acid (0·92 g.) was converted into the methyl ester by diazomethane in the usual way. The ester, in pentyl alcohol (10 c.c.), was refluxed with 100% hydrazine hydrate (5 c.c.) for 24 hr., then poured into water (100 c.c.). After the pentyl alcohol had been removed by steam-distillation, the *hydrazide* (0·82 g.) was collected; it formed needles, m. p. 148—149°, from ethanol (Found : C, 79·0; H, 5·9. $C_{19}H_{16}ON_2$ requires C, 79·1; H, 5·6%).

A solution of the hydrazide (0·68 g.) in acetic acid (6 c.c.) was cooled to 0°, and sodium nitrite (0·10 g.) in water (1 c.c.) added. After 2·5 hr. at room temperature, water (25 c.c.) was added and the crude azide collected. The latter was refluxed for 2 hr. with concentrated hydrochloric acid (6 c.c.) and acetic acid (6 c.c.). Dilution with water gave a solid, which on recrystallisation from methanol afforded, probably, 7-*phenylphenanthridone* (XVII) (0·05 g.), needles, m. p. 222° (Found : C, 84·3; H, 5·3; N, 5·0. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8; N, 5·2%). The infrared spectrum (in Nujol) showed bands at 3424 (NH) and 1685 $cm.^{-1}$ (CO·NH).

The mother-liquors were diluted with water, basified, and extracted with ethyl acetate, and the extracts dried and evaporated. The residue was taken up in dry ether and a stream of hydrogen chloride passed in. The material which separated was collected and boiled for 30 min. with methanol (25 c.c.) and 10% aqueous sodium hydroxide (5 c.c.). Dilution with water gave 2′-amino-*p*-terphenyl (0·18 g.), prisms, m. p. 171—172°, from ethanol (Found : C, 87·5; H, 5·7; N, 5·6. Calc. for $C_{18}H_{15}N$: C, 88·1; H, 6·2; N, 5·7%); Basford [8] reports m. p. 169°. The benzoate crystallised from ethanol as needles, m. p. 148° (Found : N, 4·0. Calc. for $C_{25}H_{19}ON$: N, 4·0%); Basford [8] gives m. p. 144°.

3-*Cyano*-2 : 5-*diphenyl*cyclo*hex*-2-*en*-1-*one* (XIX).—A solution of 3-methoxy-2 : 5-diphenyl-*cyclo*hex-2-en-1-one (1 g.) in acetone cyanohydrin (10 c.c.), containing 0·2 c.c. of saturated methanolic potassium hydroxide, was set aside overnight and then poured into water (100 c.c.). 3-*Cyano*-2 : 5-*diphenyl*cyclo*hex*-2-*en*-1-*one* (0·93 g.) crystallised from benzene–light petroleum as prisms, m. p. 148—149° (Found, after drying at 110°/0·1 mm. : C, 83·0; H, 5·4; N, 5·6. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5; N, 5·1%).

3-*Cyano*-2 : 5-*diphenyl*cyclo*hex*-2-*en*-1-*ol* (XX).—To the cyano-ketone (1·6 g.) in methanol (50 c.c.) was added potassium borohydride (1 g., 3 mol.) in water (10 c.c.). After 5 hr., the solution was poured into water and the precipitated solid (1·2 g.) collected. 3-*Cyano*-2 : 5-*diphenyl*cyclo*hex*-2-*en*-1-*ol* formed prisms, m. p. 157—158°, from benzene–light petroleum (Found : C, 82·6; H, 6·4; N, 4·8. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2; N, 5·1%).

Action of Diazomethane on Ethyl 2 : 4-*Dioxo*-3 : 6-*diphenyl*cyclo*hexanecarboxylate.*—The dione ester (5 g.), treated with ethereal diazomethane in the usual way, furnished an *enol ether* (1·4 g.), blades, m. p. 137—138° (from benzene–light petroleum) (Found : C, 74·9; H, 6·2. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%). Evaporation of the mother-liquors gave an oil (3·2 g.).

The oil (3·2 g.) was dehydrogenated by sulphur (0·3 g.) at 260°, and the oily product dissolved in ethyl acetate. Extraction with sodium carbonate solution yielded 2 : 5-diphenyl*cyclo*hexane-1 : 3-dione (0·05 g.). The uncrystallisable material remaining in the organic layer was hydrolysed with concentrated hydrochloric acid and the product taken up in ether. Extraction with aqueous sodium carbonate and sodium hydroxide gave 5-oxo-3 : 6-diphenylhexanoic acid (0·1 g.) and 2′ : 6′-dihydroxy-*p*-terphenyl (0·18 g.) respectively.

The crystalline enol ether (2·4 g.) was dehydrogenated by sulphur, and, after removal of 2 : 5-diphenyl*cyclo*hexane-1 : 3-dione (0·09 g.) as before, the product was treated with dimethyl sulphate in refluxing sodium hydroxide solution. Filtration gave a semisolid material, which on trituration with benzene, afforded 2′ : 6′-dimethoxy-*p*-terphenyl (0·18 g.). Acidification of the filtrate gave more 2 : 5-diphenyl*cyclo*hexane-1 : 3-dione (0·05 g.).

5-*Oxo*-3 : 6-*diphenylhexanoic Acid* (XXII).—Ethyl 2 : 4-dioxo-3 : 6-diphenyl*cyclo*hexane-carboxylate (2 g.) was refluxed with concentrated hydrochloric acid (50 c.c.) and acetic acid

(50 c.c.) for 10 hr. Evaporation yielded the *hexanoic acid* (1·4 g.), prisms, m. p. 107—108° (from benzene–light petroleum) (Found : C, 76·5; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

2′-Hydroxy-5′(?)-phenylazo-p-*terphenyl* (XXV; R = Ph·N:N).—A solution of 2′-hydroxy-*p*-terphenyl (2 g.) in ethanol (200 c.c.) was mixed with sodium acetate (8 g.) in water (10 c.c.), cooled to 0°, and treated with aqueous benzenediazonium chloride (from 0·74 g. of aniline). On dilution with water (100 c.c.) there separated dark brown material which was removed by filtration. Further dilution then gave *2′-hydroxy-5′(?)-phenylazo*-p-*terphenyl*, orange blades, m. p. 159° (from benzene–light petroleum) (Found, after drying at 78°/0·1 mm. : C, 80·7; H, 5·2; N, 7·7. $C_{24}H_{18}ON_2,\frac{1}{2}H_2O$ requires C, 80·2; H, 5·3; N, 7·8. Found, after drying at 110°/0·1 mm. : C, 81·9; H, 5·1. $C_{24}H_{18}ON_2$ requires C, 82·1; H, 5·2%).

5′(?)-Acetamido-2′-hydroxy-p-*terphenyl* (XXV; R = NHAc).—The foregoing azo-compound (0·9 g.) was added during 30 min. to a vigorously shaken mixture of zinc (2 g.), acetic acid (5 c.c.), and acetic anhydride (4 c.c.) at 0°. After 30 minutes' shaking, the solid was removed and the filtrate evaporated. *5′(?)-Acetamido-2′-hydroxy*-p-*terphenyl* (0·4 g.) crystallised from benzene as plates, m. p. 209—210° (Found : C, 78·6; H, 5·4; N, 4·9. $C_{20}H_{17}O_2N$ requires C, 79·2; H, 5·6; N, 4·6%). The infrared spectrum, measured in tetrahydrofuran, showed maxima at 3490 (OH), 3314 (NH), 1689, and 1530 cm.$^{-1}$ (NAc).

No crystalline compounds were obtained from the acetamido-compound by hydrochloric acid.

Reaction of 2 : 6′-Dihydroxy-p-*terphenyl with Diazomethane*.—The compound (1·1 g.) in methanol (20 c.c.) at 0° was treated with excess of ethereal diazomethane overnight. The solution was then washed with aqueous sodium hydroxide and water, dried ($MgSO_4$), and evaporated. The *product* (0·9 g.) formed needles, m. p. 135—136°, from benzene–light petroleum (Found : C, 75·2; H, 6·1; N, 4·2; OMe, 15·1. $C_{21}H_{21}O_3N$ requires C, 75·2; H, 6·3; N, 4·2; 2OMe, 18·5%), $\lambda_{max.}$ 263·5 mμ (ε 21,400), $\nu_{max.}$ 3324 (m), 2722 (w), 2342 (w), 1704 (s), 1614 (m), 1523 (m), 1397 (w), 1335 (w), 1304 (w), 1253 (m), 1232 (m), 1206 (w), 1164 (w), 1126 (s), 1071 (s), 928 (m), 875 (w), 852 (m), 760 (s), 755 (s), 721 (m), 697 (s) (s = strong, m = medium, w = weak).

2′ : 6′-Dimethoxy-p-*terphenyl* (XXIII).—2′ : 6′-Dihydroxy-*p*-terphenyl (1·1 g.) was refluxed with 2N-aqueous sodium hydroxide (11 c.c.) and dimethyl sulphate (2·1 c.c.) for 2 hr., more of the reagents (11 c.c. and 2·1 c.c. respectively) being added after 1 hr. The excess of dimethyl sulphate was destroyed by boiling sodium hydroxide solution, and the product (1·2 g.) collected. *2′ : 6′-Dimethoxy*-p-*terphenyl* crystallised from light petroleum as plates, m. p. 168—169° (Found : C, 82·9; H, 6·5. $C_{20}H_{18}O_2$ requires C, 82·8; H, 6·2%). This compound was also obtained by methylation of the crude dehydrogenation product of 3-methoxy-2 : 5-diphenyl-*cyclo*hex-2-en-1-one.

3′-Bromo-2′ : 6′-dihydroxy-p-*terphenyl* (XXVI; R = H).—Bromine (0·1 g., 1 mol.) in carbon tetrachloride (1 c.c.) was added to 2′ : 6′-dihydroxy-*p*-terphenyl (0·5 g.) in carbon tetrachloride (50 c.c.). Evaporation furnished the *bromo-compound*, needles, m. p. 124—125° (from light petroleum) (Found : Br, 23·4. $C_{18}H_{13}O_2Br$ requires Br, 23·5%).

3′ : 5′-Dibromo-2′ : 6′-dihydroxy-p-*terphenyl* (XXVI; R = Br).—To the preceding compound (0·21 g.) in carbon tetrachloride (20 c.c.) was added bromine (0·1 g., 1 mol.) in carbon tetrachloride (1 c.c.), and the mixture refluxed for 15 min. Evaporation yielded the *dibromo-compound*, plates, m. p. 137° (from light petroleum) (Found : C, 51·2; H, 2·9. $C_{18}H_{12}O_2Br_2$ requires C, 51·5; H, 2·9%).

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694. *The Kinetics of Oxidation of Bromide Ion in Aqueous Nitric Acid.*

By JEAN V. L. LONGSTAFF.

The kinetics of oxidation of bromide ion in aqueous nitric acid (2·4—8·0M), and in sulphuric acid and perchloric acid containing some nitrous acid and some nitric acid, have been investigated. The order of the reaction is 1·5 with respect to " analytical " nitrous acid and unity with respect to bromide. The kinetic data indicate that the rate-determining step is the decomposition or rearrangement of a complex $[N_2O_3BrH]^+$.

LITTLE work has been reported on the oxidation of bromide by nitrous acid or nitrous oxides and apparently none on its oxidation by nitric acid. Merton-Bingham and Posner [1] investigated the catalytic effect of nitrogen dioxide on the autoxidation of hydrogen bromide and suggested that the slow step in this reaction is the interaction of nitrosyl bromide with an intermediate Z formed according to the equation $HNO_2 + HBr \rightleftharpoons Z$. Their experimental conditions differ widely from those discussed here: in particular they used large concentrations of nitrogen dioxide and studied a system in which the gaseous and the liquid phase were in equilibrium; in the present work the concentration of " analytical " nitrous acid is initially small and the liquid phase only has been investigated.

The kinetics of the oxidation of bromide ion by aqueous nitric acid were investigated by measuring the change in the concentration of " analytical " nitrous acid and, in some experiments, the formation of bromine during the reaction. [" Analytical " nitrous acid denotes all entities which behave as nitrous acid in diazotising amines, and is referred to subsequently as nitrous acid or HNO_2 and its concentration as (HNO_2)].

Preliminary experiments had shown that an appreciable quantity of nitrous acid escapes into the vapour phase under ordinary conditions; this difficulty was overcome by taking each sample in kinetic runs from a completely filled brown-glass stoppered bottle; thus the participation in the reaction of the vapour phase was excluded.

Kinetic experiments were carried out at 25° in 2·4—8·0M-nitric acid with 0·002—0·25M-potassium (or sodium) bromide and an initial concentration of nitrous acid approximately 5×10^{-5}M. The velocity of the reaction was also measured in media containing perchloric and nitric acid or sulphuric and nitric acid.

RESULTS

No reaction takes place in the absence of nitrous acid or of nitric acid. The concentration of nitrous acid increases during the oxidation, and the order of reaction is initially 1·5 with respect to nitrous acid and unity with respect to bromide ion. The rate of formation of nitrous acid decreases as the reaction proceeds, a stable equilibrium being reached, the position of which depends on the initial concentrations of nitrous acid and of bromide ion, and on the composition of the medium. The order of the reaction with respect to nitrous acid is illustrated by Fig. 1 in which $(HNO_2)^{-0·5}$ is plotted against time (t) for experiments in 4·8M-nitric acid; straight

TABLE 1. *Reaction in 4·8M-nitric acid.*

[KBr] (M)	0·01	0·008	0·006	0·004	0·002
k' (l.$^{0·5}$ mole$^{-0·5}$ min.$^{-1}$)	0·86	0·596	0·50	0·31	0·17
k (l.$^{1·5}$ mol.$^{-1·5}$ min.$^{-1}$)	86	75	83	78	85

lines are obtained initially (*i.e.*, in the region over which the percentage change in concentration of bromide is small); values of k' in $d(HNO_2)/dt = k'(HNO_2)^{1·5}$ can be obtained from the slopes of these lines and are given in Table 1. The first order with respect to bromide is shown by the values of $k = k'/[Br^-]$.

[1] Merton-Bingham and Posner, *J. Amer. Chem. Soc.*, 1955, **77**, 3634.

Evaluation of the more accurate rate equation:

$$\frac{-2}{[Br^-]_0(HNO_2)^{0.5}} + \frac{4}{[2Br^-]^{1.5}} \ln \frac{[Br^-]_0^{0.5} + (2HNO_2)^{0.5}}{[Br^-]_0^{0.5} - (2HNO_2)^{0.5}} = kt + \text{Constant}$$

(where $[Br^-]_0$ is the initial concentration of bromide) which is obtained by integration of $d(HNO_2)/dt = k(HNO_2)^{1.5}[Br^-]$ leads to virtually the same values for the velocity constant.

The value of k is independent of the initial concentration of nitrous acid, *e.g.* (in 5·6M-nitric acid):

[KBr] (M)	k' ($l.^{0.5}$ mole$^{-0.5}$ min.$^{-1}$)	k ($l.^{1.5}$ mole$^{-1.5}$ min.$^{-1}$)	Initial (HNO_2) (10^{-5}M)
0·006	2·08	362	12
0·006	2·30	383	1

The rate of the reaction is very strongly dependent on the concentration of nitric acid (Table 2). In greater than 5·6M-nitric acid the reaction takes place so rapidly—even when the concentration of bromide is reduced to 0·0002M—that it is not possible to obtain accurately the velocity constant at 25°, and the values for 6·4M- and 8·0M-nitric acid are included in the Table

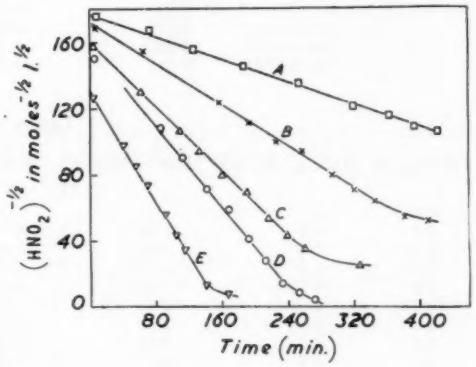

FIG. 1. *Variation of* $(HNO_2)^{-0.5}$ *with time for reaction in* 4·8M-*nitric acid.*

A, 0·002M-KBr. *D*, 0·008M-KBr.
B, 0·004M-KBr. *E*, 0·01MK-Br.
C, 0·006M-KBr.

only as indications of the order of magnitude. A plot of log k against log a_{HNO_2} gives approximately a straight line with slope 1·5, indicating that k is proportional to $(a_{HNO_2})^{1.5}$. The values of a_{HNO_2} given in Table 2 are obtained from the partial pressures of HNO_2 and H_2O above aqueous nitric acid at 25° given by Klemenc and Nagel [2] and from the activity coefficients of nitric acid measured by Abel, Redlich, and von Lengyel.[3]

TABLE 2.

$[HNO_2]$ (M)	[KBr] (M)	k' ($l.^{0.5}$ mole$^{-0.5}$ min.$^{-1}$)	k ($l.^{1.5}$ mole$^{-1.5}$ min.$^{-1}$)	a_{HNO_2}
2·4	0·25	0·66	2·6	5
3·2	0·02	0·15	7·5	10·5
4·8	0·002—0·01	—	80 (mean)	45
5·6	0·006	2·30	383	93
6·4	0·0002	0·230	1150	400
8·0	0·0002	5·16	25,800	2200

The range of validity of the order 1·5 with respect to nitrous acid and the equilibrium position also vary with the concentration of nitric acid, the conversion of bromide into bromine going almost to completion in 8·0M-nitric acid, to ~70% in 5·6M-nitric acid, to ~60% in 4·8M-nitric acid and to ~30% in 3·2M-nitric acid.

The reaction is accelerated by sodium nitrate and, to a greater extent, by sodium perchlorate (Table 3).

The effects of the concentrations of hydrogen and of nitrate ion on the rate of the reaction at constant ionic strength were investigated, the media for these experiments being prepared by mixing calculated quantities of nitric acid, perchloric acid, sodium nitrate, and sodium

[2] Klemenc and Nagel, *Z. anorg. Chem.*, 1928, **155**, 257.
[3] Abel, Redlich, and von Lengyel, *Z. phys. Chem.*, 1928, **32**, 189.

perchlorate. The results of four sets of experiments in which the concentration of nitrate is varied at constant hydrogen-ion concentration ($[H^+] = 4{\cdot}8$, $3{\cdot}2$, $2{\cdot}4$, and $1{\cdot}6$M severally) and at constant ionic strength (μ 4·8) are summarised in Table 4. It can be seen that, at a given concentration of hydrogen ion, the rate of reaction increases as the concentration of nitrate is decreased from 4·8M to 1·0M and, moreover, that this trend increases with the acidity of the medium.

TABLE 3.

$[HNO_3]$ (M)	Added salt	[KBr] (M)	k' ($l.^{0.5}$ mole$^{-0.5}$ min.$^{-1}$)	$k = k'/[Br^-]$ ($l.^{1.5}$ mole$^{-1.5}$ min.$^{-1}$)
3·2	0	0·02	0·15	7·5
,,	1·6M-$NaClO_4$	0·02	0·78	39
,,	,,	0·01	0·39	39
,,	,,	0·01	0·41	41
,,	,,	0·008	0·305	38
,,	1·6M-$NaNO_3$	0·02	0·47	23·5
,,	,,	0·02	0·49	24·5
,,	,,	0·01	0·25	25
2·4	0	0·25	0·66	2·6
,,	2·4M-$NaClO_4$	0·02	0·39	19·5
,,	,,	0·01	0·21	21
,,	2·4M-$NaNO_3$	0·02	0·21	10·5
1·6	3·2M-$NaClO_4$	0·02	0·12	6
,,	3·2M-$NaNO_3$	0·02	0·13	6·5

TABLE 4.

$[HNO_3]$ (M)	$[HClO_4]$ (M)	k' ($l.^{0.5}$ mole$^{-0.5}$ min.$^{-1}$)	[KBr] (M)	k ($l.^{1.5}$ mole$^{-1.5}$ min.$^{-1}$)	$k/[NO_3^-]^{0.5}$ ($l.^2$ mole^{-2} min.$^{-1}$)
		$[H^+] = 4{\cdot}8$M			
4·8	0	—	—	80 (mean value)	36·5
3·2	1·6	1·98	0·01	198	109
2·4	2·4	2·26	0·006	377	243
1·6	3·2	1·17	0·002	585	462
1·01	3·79	2·52	0·0025	1010	1010
0·74	4·06	2·87	0·0025	1150	1340
0·45	4·35	2·65	0·0025	1060	1580
0·1	4·7	2·04	0·0025	816	2580
0	4·8	0	0·002	0	—

$[HNO_3]$ (M)	$[HClO_4]$ (M)	$[NaNO_3]$ (M)	$[NaClO_4]$ (M)	Total $[NO_3^-]$ (M)	k ($l.^{1.5}$ mole$^{-1.5}$ min.$^{-1}$)	$k/[NO_3^-]^{0.5}$ ($l.^2$ mole^{-2} min.$^{-1}$)
			$[H^+] = 3{\cdot}2$M			
3·2	0	1·6	0	4·8	24	10·9
3·2	0	0	1·6	3·2	36	20·1
2·0	1·2	0	1·6	2·4	56	36·1
1·0	2·2	0	1·6	1·0	90	90
			$[H^+] = 2{\cdot}4$M			
2·4	0	2·4	0	4·8	10·5	4·84
2·4	0	0·8	1·6	3·2	16	8·9
2·4	0	0	2·4	2·4	20	12·9
1·0	1·4	2·4	0	1·0	25	25
			$[H^+] = 1{\cdot}6$M			
1·6	0	3·2	0	4·8	6·5	2·96
1·6	0	0	3·2	1·6	6	5·14
0·48	1·12	0	4·2	0·48	8·5	12·2

Experiments at $[H^+] = 4{\cdot}8$M, $\mu = 4{\cdot}8$, in which nitrate ion was progressively replaced by bisulphate ion, were also carried out (Table 5). The rate of the reaction again increases as the nitrate concentration is reduced, but the percentage increase is smaller.

The two sets of experiments in which the hydrogen-ion concentration is 4·8M, $\mu = 4{\cdot}8$, and the concentration of nitrate ion is progressively diminished (by replacement with either bisulphate ion or with perchlorate ion) were extended down to $[NO_3^-] = 0{\cdot}1$M (Tables 4 and 5). In both cases, the velocity constant passes through a maximum value. With the initial concentrations of bromide ion and of nitrous acid investigated, no increase in the concentration of nitrous acid and no formation of bromine take place when all the nitrate ion is replaced by

perchlorate ion or by bisulphate ion (*i.e.*, in 4·8M-perchloric or -sulphuric acid). Table 6 shows the effect on the rate of reaction of varying the hydrogen-ion concentration at constant ionic strength ($\mu = 4·8$) and at constant nitrate-ion concentration ($[NO_3^-] = 4·8$, 3·2, 2·4, and 0·45M severally). The rate of the reaction increases with the hydrogen-ion concentration, the increase being greater the smaller the concentration of nitrate. Plots of log k against log $[H^+]$ for these sets of experiments give approximately straight lines, the slopes of which vary from 2·5 to 4·5.

TABLE 5. *Experiments at* $[H^+] = 4·8$M, $\mu = 4·8$.

HNO_3 (M)	H_2SO_4 (M)	KBr (M)	k' ($l.^{0·5}$ mole$^{-0·5}$ min.$^{-1}$)	k ($l.^{1·5}$ mole$^{-1·5}$ min.$^{-1}$)	$k'' = k/[NO_3^-]^{0·5}$ ($l.^{2}$ mole^{-2} min.$^{-1}$)
4·8	0	—	—	80	36·5
3·2	1·6	0·01	1·96	196	109
2·4	2·4	0·006	1·80	300	194
1·6	3·2	0·002	0·97	485	384
1·0	3·8	0·002	1·11	550	550
1·0	3·8	0·004	2·2	550	550
0·8	4·0	0·002	1·12	560	618
0·5	4·3	0·002	1·4	700	989
0·3	4·5	0·002	1·25	625	1140
0·2	4·6	0·002	1·11	550	1230
0·1	4·7	0·002	0·9	450	1430
0	4·8	0·002	0	0	—

Some experiments were carried out in which part of the water of the reaction mixture was replaced by acetic acid; the rate of the reaction increased with decrease in the concentration of water (Table 7).

TABLE 6.

$[NO_3^-] = 4·8$M	$[HNO_3]$ (M)	1·6	2·4	3·2	4·8			d log k/d log $[H^+] = 2·5$
	$[NaNO_3]$ (M)	3·2	2·4	1·6	0			
	k ($l.^{1·5}$ mole$^{-1·5}$ min.$^{-1}$)	6·5	10·5	24	80			
$[NO_3^-] = 3·2$M	$[NaNO_3]$ (M)	0·8	0	0				d log k/d log $[H^+] = 3·6$
	$[HNO_3]$ (M)	2·4	3·2	3·2				
	$[NaClO_4]$ (M)	1·6	1·6	0				
	$[HClO_4]$ (M)	0	0	1·6				
	$[H^+]$ (M)	2·4	3·2	4·8				
	k ($l.^{1·5}$ mole$^{-1·5}$ min.$^{-1}$)	16	36	196				
$[NO_3^-] = 2·4$M	$[HNO_3]$ (M)	2·4	2·4	2·4	2·4	2·4	2·4	$\frac{\text{d log } k}{\text{d log } [H^+]} = 4·1$
	$[HClO_4]$ (M)	0	0·4	0·8	1·2	1·8	2·4	
	$[NaClO_4]$ (M)	2·4	2·0	1·6	1·2	0·6	0	
	$[H^+]$ (M)	2·4	2·8	3·2	3·6	4·2	4·8	
	k ($l.^{1·5}$ mole$^{-1·5}$ min.$^{-1}$)	20	39·5	53	90	200	346	
$[NO_3^-] = 0·45$M	$[HNO_3]$ (M)	0·45	0·45					d log k/d log $[H^+] = 4·4$
	$[HClO_4]$ (M)	1·15	4·35					
	$[NaClO_4]$ (M)	3·2	0					
	$[H^+]$ (M)	1·6	4·8					
	k ($l.^{1·5}$ mole$^{-1·5}$ min.$^{-1}$)	8·5	1060					

TABLE 7. *Experiments in* 4·8M-*nitric acid.*

Acetic acid (M)	0	0·85	1·7	3·4	5·1
k ($l.^{1·5}$ mole$^{-1·5}$ min.$^{-1}$)	80	200	365	1330	6100

The stoicheiometry of the reaction was determined by measurement of the rate of formation of bromine in some experiments. Considerable difficulty was experienced in finding a suitable method for the estimation of bromine, particularly as the total concentration formed in an experiment is small, but spectroscopic measurement of the concentration of bromine in a few runs showed that its rate of formation is equal to the rate of increase of concentration of nitrous acid (Table 8).

TABLE 8.

Time (min.)	(HNO_2) $(10^{-3}M)$ measured	(HNO_2) $(10^{-3}$ M) interpolated	$[Br_2]$ $(10^{-3}M)$	Time (min.)	$(HNO_2)(10^{-3}$ M) measured	(HNO_2) $(10^{-3}M)$ interpolated	$[Br_2]$ $(10^{-3}$ M)
3	0·058	—	—	89	3·95	—	—
26	0·115	—	—	90	—	3·9	4·0
48	0·263	—	—	106	4·3	—	—
52	—	0·3	0·3	108	—	—	4·2
71	1·5	—	—	135	4·3	—	4·2
77	—	2·2	2·1				

TABLE 9.

Temp.	$[HNO_3]$ (M)	[KBr] (M)	k' ($l.^{0·5}$ $mole^{-0·5}$ $min.^{-1}$)	$k = k'/[Br^-]$ ($l.^{1·5}$ $mole^{-1·5}$ $min.^{-1}$)
0°	8	0·002	1·55	775
,,	6·4	0·01	0·71	71
,,	6·4	0·01	0·65	65
,,	5·6	0·024	0·48	20
,,	5·6	0·024	0·36	15
15	5·6	0·01	1·062	106
,,	4·8	0·04	1·11	27·8
35	5·6	0·0012	1·08	900
,,	5·6	0·002	1·75	875
,,	4·8	0·006	1·55	258

The results of experiments in 3·2, 4·8, and 5·4M-nitric acid at temperatures in the range 0—35° are summarised in Table 9. For each medium, log k is directly proportional to $1/T$, and the activation energies are 23, 21·2, and 18·43 kcal. $mole^{-1}$ respectively.

DISCUSSION

Bromide ion is not oxidised by nitric acid in the absence of nitrous acid and the orders of the reaction with respect to nitrous acid and bromide are respectively 1·5 and unity; therefore, entities derived from nitrous acid and bromide ion take part in the rate-determining step. Although replacing some of the nitric acid by perchloric or sulphuric acid markedly increases the velocity, no reaction takes place (in the concentration range investigated) in the absence of nitric acid. Since (HNO_2) increases during the reaction, one function of nitric acid must be to oxidise a product of the reaction between bromide ion and nitrous acid (probably nitric oxide) and thus to provide more nitrous acid for reaction. An entity derived from nitric acid in the presence of nitrous acid (but not in its absence) may also be directly involved.

The following equilibria (which are not all independent of each other) are known or assumed to exist in aqueous nitric acid containing analytical nitrous acid: [4]

$$H_2O + HNO_3 \rightleftharpoons OH_3^+ + NO_3^-$$
$$HNO_2 + H^+ + NO_3^+ \rightleftharpoons N_2O_4 + H_2O$$
$$N_2O_4 \rightleftharpoons 2NO_2$$
$$N_2O_4 \rightleftharpoons NO^+ + NO_3^-$$
$$HNO_2 + OH_3^+ \rightleftharpoons H_2NO_2^+ + H_2O$$
$$H_2NO_2^+ \rightleftharpoons NO^+ + H_2O$$
$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O$$
$$N_2O_3 \rightleftharpoons NO + NO_2$$
$$NO^+ + NO_2 \rightleftharpoons N_2O_3^+$$

[4] Abel, Schmid, and Stein, *Z. Elektrochem.*, 1930, **36**, 692; Goulden and Millen, *J.*, 1950, 2620; Hughes, Ingold, and Reed, *J.*, 1950, 2430.

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In the presence of bromide ion, the following additional equilibrium exists :

$$HNO_2 + H^+ + Br^- \rightleftharpoons NOBr + H_2O$$

In aqueous sulphuric acid, aqueous perchloric acid, and 2—8M-aqueous nitric acid (*i.e.*, in all the media used in the present work), the bulk of the " analytical " nitrous acid is present as molecular nitrous acid.[5] The rate-determining step must therefore involve an entity or entities stoicheiometrically related to $[HNO_2]$ in the ratio 1·5 : 1 and to $[Br^-]$ in the ratio 1 : 1 and very probably dependent in some way on nitric acid. The dependence on $[HNO_2]^{1.5}$ indidates very strongly that, in addition to an entity stoicheiometrically related to (HNO_2) in the ratio 1 : 1, nitrogen dioxide takes part (either in the rate-determining step or in the formation of an entity involved in it), since nitrogen dioxide is the only entity proportional to $(HNO_2)^{0.5}$.

The following equations represent possible reaction schemes compatible with $k \propto (HNO_2)^{1.5}[Br^-]$:

(1)	$NOBr + NO_2 \longrightarrow N_2O_3 + Br$	Slow
	$2Br \longrightarrow Br_2$	Fast
(2)	$NOBr + NO_2 \longrightarrow N_2O_3Br$	Slow
	$N_2O_3Br + Br^- \longrightarrow Br_2 + NO + NO_2^-$	Fast
(3)	$N_2O_3^+ + Br^- \longrightarrow N_2O_3 + Br$	Slow
	$2Br \longrightarrow Br_2$	Fast
(4)	$N_2O_3^+ + Br^- \longrightarrow N_2O_3Br$	Slow
	$N_2O_3Br + Br^- \longrightarrow NO + NO_2^- + Br_2$	Fast

Each of the rate-determining steps in the above schemes—and in fact any step involving one molecule of nitrogen dioxide—varies as $(a_{HNO_2})^{0.5}$ Experiments in aqueous nitric acid, however, show that k is proportional to $(a_{HNO_2})^{1.5}$. The very marked increase in rate when nitrate ion is partially replaced by perchlorate ion or bisulphate ion also points to the stronger dependence on acidity than occurs in the above schemes.

A rough estimate of the equilibrium concentration of bromine atoms (which is an upper limit for [Br]) can be made from thermodynamic data [6] ($Br_2 \longrightarrow 2Br$; $2Br^- \longrightarrow 2Br + 2e$; $NO_2 + H^+ + e \longrightarrow HNO_2$) and is found to be so small that the rate of combination of bromine atoms with zero activation energy will not effectively compete with the rate of reaction of bromine atoms with nitrous acid unless the activation energy for the latter is of the order of 15 kcal. mole^{-1}. This is not likely. Reaction of bromine atoms with nitrous acid will therefore be fast compared with combination of 2 bromine atoms, so that schemes (1) and (3) would not be compatible with $k \propto (HNO_2)^{1.5}$. It is possible to calculate, fairly reliably, by using known activity coefficients and equilibrium constants [4, 6] ($HNO_2 + HNO_3 \longrightarrow N_2O_4 + H_2O$; $N_2O_4 \rightleftharpoons 2NO_2$; $HNO_2 + HBr \rightleftharpoons NOBr + H_2O$), the dependence of k upon a_{HNO_3} and a_{H_2O} for mechanisms in which the rate-determining step involves reaction of nitrosyl bromide with nitrogen dioxide. The calculated variation of k with a_{HNO_3} differs very considerably from that obtained experimentally, providing additional evidence against schemes (1) and (2).

To account for the strong dependence of the rate of the reaction on acidity, it appears

[5] Longstaff and Singer, *J.*, 1954, 2610; Singer and Vamplew, *J.*, 1955, 3971.
[6] Latimer, " Oxidation Potentials," Prentice-Hall, New York, 1938.

to be necessary to introduce an additional hydroxonium ion into the mechanism; this can result in the formation of either a protonated entity or Br_2^+ as in the following equations:

(5)	$N_2O_3Br + OH_3^+$ or $N_2O_3^+ + Br^- + OH_3^+$ or $NOBr + NO_2 + OH_3^+$ $\rightleftharpoons N_2O_3BrH^+ + H_2O$	Rapidly established equilibrium
	$N_2O_3BrH^+ \longrightarrow X^+ + Y$	Rate-determining
	$X^+ + Br^- \longrightarrow Br_2 + NO +$ other products	Fast
	$2NO + HNO_3 + H_2O \longrightarrow 3HNO_2$	Fast
(6)	$N_2O_3Br + OH_3^+$ or $N_2O_3^+ + Br^- + OH_3^+$ or $NOBr + NO_2 + OH_3^+$ $\longrightarrow Br^+ + H_2O + NO + HNO_2$	Slow
	$Br^+ + Br^- \longrightarrow Br_2$	Fast
	$2NO + H_2O + HNO_2 \longrightarrow 3HNO_2$	Fast

The protonation of a neutral molecule is usually fast [7] and not likely to be rate-determining. Therefore, if $N_2O_3BrH^+$ is involved in the reaction, the slow step might be

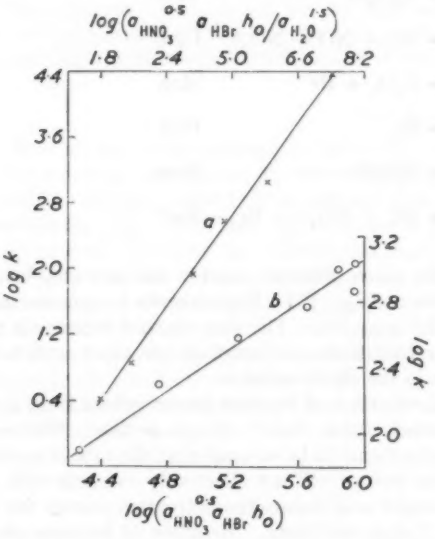


FIG. 2.

(*a*) *Relation of* log *k with* log $(a_{HNO_3}^{0.5} . a_{HBr} . h_0/a_{H_2O}^{1.5})$ *for reaction in aqueous nitric acid (left hand and top scales).*

(*b*) *Relation of* log *k with* log $(a_{HNO_3}^{0.5} . a_{HBr} . h_0)$ *for reaction in nitric–perchloric acid (right hand and lower scales).*

either the rearrangement of this protonated entity to form a less easily deprotonated complex or the formation of hypobromous acid:

$N_2O_3BrH^+ \longrightarrow HOBr + N_2O_2^+$	Slow
$HOBr + HBr \longrightarrow Br_2 + H_2O$	Fast

Although, at first sight, the introduction of a hydroxonium ion may appear rather implausible, the elimination of HNO_2 and NO from $N_2O_3BrH^+$ is thermodynamically more favourable than the elimination of NO and NO_2^- from N_2O_3Br ($HNO_2 \longrightarrow NO_2^- + H^+$; $\Delta G = 4600$ cal.). Also, since NO_2 can associate with NO_2, NO, and NO^+, it is plausible that it can associate with NOBr to form N_2O_3Br. This entity should be more basic, and

[7] Long and Paul, unpublished review on acidity functions.

therefore have a greater tendency to attract H^+, than either N_2O_3 or N_2O_4, since it contains two electron-attracting groups (NO_2 and Br) and since Br is more electron-attracting than NO_2. The equilibrium concentration of Br^+ can be estimated from thermodynamic data [6,8] ($Br^- + H_2O \longrightarrow 2e + Br^+ + H_2O$) and is so small that reaction between Br^+ and Br^- with zero energy of activation could not account for the observed rate of reaction. A rough estimate of the equilibrium concentration of $N_2O_3BrH^+$ can be made if it is assumed that the frequency factors for the bimolecular reactions involved are normal and that the activation energies are zero. The concentation of $N_2O_3BrH^+$ is such that its reaction with Br^- would lead to a velocity 10—100 times smaller than the observed velocity.

The proposed mechanism can therefore be summarised:

$$\tfrac{3}{2}HNO_2 + \tfrac{1}{2}HNO_3 + HBr + H^+ \rightleftharpoons N_2O_3BrH^+ + \tfrac{3}{2}H_2O$$

$$N_2O_3BrH^+ \longrightarrow X^+ + Y \qquad \text{Rate-determining step}$$

$$X^+ + Br^- \longrightarrow Br_2 + NO + \text{other products} \qquad \text{Fast}$$

$$2NO + H_2O + HNO_3 \longrightarrow 3HNO_2 \qquad \text{Fast}$$

The overall reactions is:

$$2HBr + HNO_3 \longrightarrow HNO_2 + Br_2 + H_2O$$

which is consistent with the observed stoicheiometry of the reaction.

The velocity of a protonation in which a molecule of water is not present in the activated complex is known to be linearly correlated with the h_0 function of the medium.[8] Hence for the above mechanism,

$$k = \text{Const.}a_{HNO_2}{}^{0.5}a_{HBr}h_0/a_{H_2O}{}^{1.5}$$

h_0 data for aqueous nitric acid media are available [9] and, if it is assumed that $f_{Br^-} = f_{NO_3^-}$, there is a linear relation between log k and log $(a_{HNO_2}{}^{0.5}a_{HBr}h_0/a_{H_2O}{}^{1.5})$ for the experiments in aqueous nitric acid (Fig. 2). The slope of the line is $\simeq 0.7$ instead of the theoretical unity, but in view of the approximation made this is not a serious discrepancy and these results are compatible with the above mechanism.

Any attempt to estimate the activities of chemical species in, and the h_0 function of, mixtures of perchloric and nitric acid is necessarily speculative. One might make the following additional assumptions:

(*a*) $H^0_{\text{medium}} = (M_1H^0_p + M_2H^0_n)/(M_2 + M_1)$ where H^0_p and H^0_n are respectively the values of the acidity function of perchloric acid and of nitric acid at molarity $M_1 + M_2$.

(*b*) $a_{HX} = a_{HNO_3} + a_{HClO_4} = m_p{}^2\gamma_p{}^2 + m_n{}^2\gamma_n{}^2$ where m_p is the molality corresponding to the concentration of perchloric acid in the medium and γ_p is the activity coefficient of perchloric acid in a $(m_p + m_n)$-solution. γ_n and m_n are similarly defined for nitric acid.

Since $[HClO_4] + [HNO_3] = [HX] = \text{Constant}$

$$\gamma_{HX} = a_{HX}/[HX] = \text{Const.}a_{HX}$$

Hence

$$a_{HNO_3} = \text{Const.}[HNO_3].a_{HX}$$

$$a_{HBr} = \text{Const.}[HBr].a_{HX}$$

(*c*) $a_{H_2O} \simeq$ constant in these media at constant ionic strength.

Again, a plot of log k against log $(a_{HNO_2}{}^{0.5}a_{HBr}h_0)$ is approximately a straight line (Fig. 2) with slope ~ 0.7. No quantitative significance can be attached to this result but it indicates that the activities of the entities involved may well vary sufficiently, as nitric is replaced by perchloric acid, to account for the very marked increase in the velocity of reaction.

[8] Bell and Gelles, *J.*, 1951, 2734.
[9] Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721.

Data on the h_0 function of nitric acid in aqueous acetic acid are not available, but the h_0 functions of perchloric and sulphuric acid are known to be very greatly increased when water is replaced by acetic acid.[8] Walker and Chadwick[10] found that the velocity of decomposition of trioxan in a molar solution of sulphuric acid in acetic acid was 2000 times as great as in aqueous M-sulphuric acid and that the velocity was linearly correlated with the h_0 function of sulphuric acid in the two media. Hence the large increase (700-fold) in velocity constant obtained here in media containing 4·8M-nitric and 5·1M-acetic acid, compared with 4·8M-aqueous nitric acid, is probably explicable in terms of the increase of the h_0 function of the medium and would be expected from the suggested mechanism.

Experimental

Materials.—" AnalaR " sulphuric acid, perchloric acid, sodium nitrite, potassium bromide, sodium bromide, and sodium nitrate, and Hopkin and Williams's sodium perchlorate were used without further purification. Nitric acid was freed from nitrous acid by passage of a current of nitrogen for 30 min. in the dark—the concentration of nitrous acid is thus reduced to approx. 1×10^{-5}M.

Determination of Nitrite and of Bromine.—The concentration of analytical nitrous acid was determined by the colorimetric method described by Shinn[11] and modified by Kershaw and Chamberlin,[12] the colour being measured on a Unicam spectrophotometer S.P. 600 at 5460 Å. Nitrite concentrations in the range 1×10^{-5} to 7×10^{-5}M can be estimated by this method: more concentrated solutions are determined after suitable dilution. The reagents are stable for several weeks; nitrate, perchlorate, and bromide do not interfere.

Bromine was determined by measurement of the absorption of the reactant solution in the region 4100—4200 Å. The control cell was filled with nitric acid of strength equal to that of the reaction medium. The extinction coefficient of bromine was found by adding 5 ml. of a standard solution of bromine (0·098M) to 495 ml. of nitric acid of suitable concentration and measuring the absorption of the solution. This solution was stable for more than 2 hr. In the region 4100—4200 Å, the absorption due to bromine is near its maximum and that due to nitrous acid (which is present in the reactant solution) is negligibly small.

Kinetic Experiments.—In order to prevent loss of gases and to exclude the effect of light, each sample in kinetic runs was taken from a completely filled brown-glass stoppered bottle. It is, of course, essential that the initial concentrations of all entities should be the same for all samples in one run, and since the required initial concentration of nitrous acid is very small (approx. 5×10^{-5}N) it is extremely difficult to ensure this if each sample is prepared separately. The reaction mixture was therefore prepared at 25° in a 250 ml. flask, by mixing calculated volumes of nitric acid, sodium or potassium bromide solution, and sodium nitrite solution, and diluting the whole to the mark with water. The reaction mixture was then poured quickly into small brown-glass stoppered bottles, completely filling each bottle. After suitable intervals 5 or 10 ml. samples were taken from the brown stoppered flasks and added to a slight excess of cooled sodium hydroxide solution, and the resultant solution was made up to a standard volume.

The colorimetric determination of nitrite was carried out on a suitable aliquot part of the solution.

In the experiments in which bromine was also measured, some of the reactant solution was poured into a stoppered cell and its absorption at 4100—4200 Å was measured immediately.

For the experiments in which $[NO_3^-]$ is varied at constant $[H^+]$ and constant ionic strength, and those in which $[H^+]$ is varied at constant $[NO_3^-]$ and constant ionic strength, the media were prepared by mixing calculated quantities of the appropriate acids and salts.

I thank Dr. K. Singer for helpful discussions and Mr. R. P. Bell, F.R.S., for constructive criticism and advice. I am also indebted to the Central Research Funds Committee of the University and to Imperial Chemical Industries Limited for grants.

Bedford College, University of London. [*Received, November 8th*, 1956.]

[10] Walker and Chadwick, *Ind. Eng. Chem.*, 1947, **39**, 974.
[11] Shinn, *Ind. Eng. Chem., Anal. Ed.*, 1941, **13**, 33.
[12] Kershaw and Chamberlin, *ibid.*, 1942, **14**, 312.

XUM

695. *The Chemistry of Fungi. Part XXVII.* The Structure of Fulvic Acid† from* Carpenteles brefeldianum.

By F. M. Dean, R. A. Eade, R. Moubasher, and Alexander Robertson.

Structure (I; R = H) is proposed for fulvic acid, the yellow acidic metabolite of *Carpenteles brefeldianum* Dodge. The chief degradation product was identical with a compound first obtained from citromycetin and now shown to be 2-acetyl-7-hydroxy-4 : 5-dimethoxyindane-1 : 3-dione and not 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid as originally proposed.[2] The nature of this product in combination with spectroscopic data provided evidence for the existence of the chromone ring in fulvic acid and the behaviour of the acid as a hemiketal together with the formation of a compound considered to be a pyridine oxide from a third ring completed the evidence on which structure (I; R = H) is based. Several other reactions and properties of fulvic acid are shown to be consistent with this formulation.

In a study of the metabolites of various species of *Penicillia*, Oxford, Raistrick, and Simonart [1] noted that, when grown on a Raulin–Thom medium, *P. griseofulvum* Dierckx produced a yellow substance which was named fulvic acid. *P. flexuosum* Dale and *P. brefeldianum* Dodge produced the same metabolite when incubated on the same medium; the latter organism, now known as *Carpenteles brefeldianum* Dodge (Shear), was used as a source of material for the present work which has resulted in the allocation of structure (I; R = H) to fulvic acid.

Oxford *et al.* established that the new metabolite had the empirical formula $C_{14}H_{12}O_8$ and, from the formation of phenolic methyl and ethyl esters by the Fischer–Speier method, concluded that a carboxyl group was present. More vigorous alkylation furnished a neutral dimethyl ether of the methyl ester, thus indicating the existence of two phenolic hydroxyl groups, in agreement with the formation of an acidic di-*O*-acetate from fulvic acid. This diacetate, however, was in reality derived from anhydrofulvic acid $C_{14}H_{10}O_7$, itself easily obtainable by sublimation of fulvic acid. These facts enabled Oxford *et al.* to perceive a close resemblance between fulvic acid and citromycetin, the yellow acidic metabolite of *P. glabrum* Wehmer, and to attach importance to the fact that anhydrofulvic acid and citromycetin were isomerides. Fulvic acid and citromycetin were observed to have the same characteristic ferric reaction and both compounds were devoid of methoxyl groups and optical activity, but citromycetin formed salts with hydrogen bromide and hydrogen iodide whereas it appeared that fulvic acid did not. In its earlier stages, our examination of fulvic acid was guided by reference to the chemistry of citromycetin, for which structure (II; R = H) has been established.[2,3,4]

Attempted crystallisation of methyl di-*O*-methylfulvate from acetic acid effected dehydration, producing methyl anhydrodi-*O*-methylfulvate identical with the ester resulting from alkylation of anhydrofulvic acid with diazomethane or methyl sulphate. Because methyl anhydrodi-*O*-methylfulvate was comparatively readily purified, it was the preferred starting point for further studies. Oxidation of this ester by permanganate under relatively stringent conditions terminated in the phthalic acid derivative (III), previously obtained by oxidation of methyl di-*O*-methylcitromycetin (II; R = Me); as before, the identity of this acid was confirmed by its conversion into the ethoxy-anhydride (IV) [4]

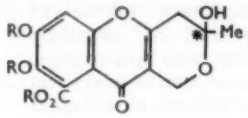
* Part XXVI, *J.*, 1957, 542.

† The use of the name fulvic acid to designate a fraction obtained by the extraction of soil has priority, but because in that context the name refers to a heterogeneous material, we prefer to adhere to the nomenclature of Raistrick's school.[1]

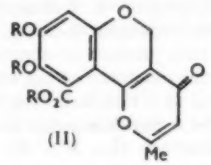
[1] Oxford, Raistrick, and Simonart, *Biochem. J.*, 1935, **29**, 1102.
[2] Robertson, Whalley, and Yates, *J.*, 1951, 2013.
[3] Mackenzie and Robertson, *J.*, 1949, 497.
[4] Robertson and Whalley, *J.*, 1949, 848; Cavill, Robertson, and Whalley, *J.*, 1950, 1031.

XUM

identical with a synthetic specimen. A second oxidation product was obtained in small amount, insufficient for further investigation, but a third is considered to be the 4-hydroxycoumarin (V; R = CO_2Me) because of its molecular formula $C_{10}H_3O_4(OMe)_3$, indifference to carbonyl reagents, acidity, pale brown ferric reaction, high decomposition point, and infrared absorption spectrum which possessed a band at 1735 cm.$^{-1}$ attributed to the methoxycarbonyl group since 4-hydroxy-6 : 7-dimethoxycoumarin (V; R = H) absorbed at, but not above, 1704 cm.$^{-1}$.



(I)



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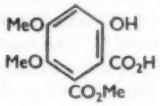

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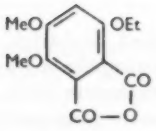

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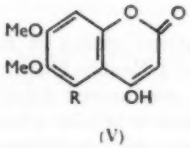

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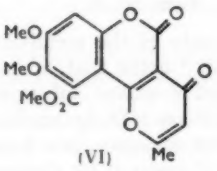

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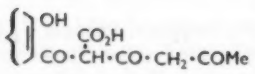

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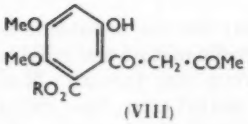

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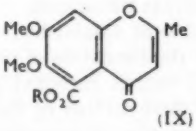

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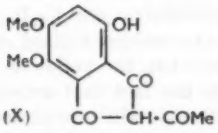
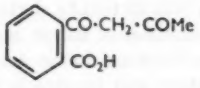
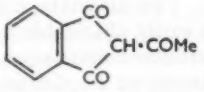


(X)



(XI)



(XII)

The oxidation of methyl di-*O*-methylcitromycetin (II; R = Me) with chromic acid gave the lactone (VI), methyl di-*O*-methylcitromycetinone, hydrolysis of which furnished several important degradation products. It was evident that one mode of hydrolysis of (VI) included fission of both heterocyclic rings giving the polyketone (VII) as an unstable intermediate from which loss of carbon dioxide and the terminal acetyl group would yield a β-diketone (VIII; R = Me) able to cyclise to the chromone ester (IX; R = Me). Although the chromone ester (IX; R = Me) was not detected in the hydrolysate of (VI), there was present an acidic substance which was considered to be the corresponding acid (IX; R = H). The same compound has now been obtained by hydrolysis of methyl anhydrodi-*O*-methylfulvate without prior oxidation. Schwerin [5] has shown that, when liberated from its salts, *o*-acetoacetylbenzoic acid (XI) spontaneously generates acetylindanedione (XII), a type of cyclisation which, if it occurred in the case of the diketone (VIII; R = H), would result in the triketone (X) instead of the chromone (IX; R = H). Although β-triketones simulate carboxylic acids in many respects and are difficult to distinguish from them, a closer scrutiny of the acidic degradation product from methyl di-*O*-methylcitromycetin and methyl anhydrodi-*O*-methylfulvate has established that this must be the acetylindanedione derivative (X) and not the chromone (IX; R = H). In keeping with its character as an *o*-hydroxy-β-diketone, the degradation product gives

[5] Schwerin, *Ber.*, 1894, **27**, 104.

(*a*) an intense purple ferric reaction distinct from the weak reddish colours given by carboxylic acids, (*b*) an oxime under conditions in which chromones are inert, and (*c*) a dimethyl ether instead of the monomethyl derivative expected from an acid having the structure (IX; R = H). Further, under conditions which destroy chromones this product, like acetylindanedione (XII), was remarkably resistant to alkaline hydrolysis. Moreover, the ultraviolet absorption spectrum differed widely from those of representative chromones, whereas the infrared absorption spectrum included bands at 1704, 1654, 1635, and 1605 cm.$^{-1}$ which tally with those shown by acetylindanedione at 1706, 1658, 1629, and 1601 cm.$^{-1}$.

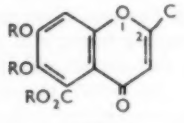
Because the β-diketone (VIII; R = H) is the parent of both (IX; R = H) and (X), further revision of the chemistry of citromycetin was not implied in the adoption of structure (X) for the acidic degradation product, and the formation of acid (III) made clear the point from which elaboration of the carbon skeleton of fulvic acid was to be continued. On the other hand, the production of the indanedione (X) obscured the question as to whether fulvic acid and its derivatives contained a chromone ring, and, in fact, a simple degradation product containing a chromone ring has not been isolated. Nevertheless, we consider that system (XIII) must be present, because fulvic acid and its derivatives do not contain a reactive carbonyl group and have ultraviolet and infrared absorption spectra strongly reminiscent of simpler chromones. In detail, the fulvates have a band between 1740 and 1754 cm.$^{-1}$ because of the methoxycarbonyl group (this frequency is rather high for an aromatic ester but is not unexpected in view of the possibility of interaction with the rigidly held neighbouring carbonyl group [6] and the possibility that steric effects might be reducing the effective conjugation of the methoxycarbonyl group with the benzene ring), at 1647 (chromone carbonyl), 1592, 1555, and 1450 cm.$^{-1}$, a pattern which may be compared with that of 6 : 7-dimethoxy-2-methylchromone having bands at 1648, 1603, 1595 (shoulder), 1511, and 1486 cm.$^{-1}$. The ultraviolet absorption spectra are discussed below. In support of the formulation of fulvic acid as a chromone, it must also be pointed out that alternatives either lead to the structure (II) already ascribed to citromycetin or must be based on a structure of type (XIV; R = H or Me) which is extremely difficult to reconcile with the spectroscopic data and the reactions and properties now to be described.

With regard to the nature of the conversion of fulvic into anhydrofulvic acid, this change, which is paralleled by the transformation of methyl di-*O*-methylfulvate into methyl anhydrodi-*O*-methylfulvate, could be effected by sublimation or merely by dissolution in hot acetic acid, and was accompanied by disappearance of the hydroxyl absorption near 3450 cm.$^{-1}$ shown by fulvates (but not by anhydrofulvates which are transparent in this region). That the labile water was not water of crystallisation was evident from the readiness with which anhydrofulvates crystallised from aqueous solvents and from the ultraviolet absorption spectra of the anhydro-compounds which showed bathochromic shifts appropriate to the introduction of a new double bond in conjugation with a chromone ring. The hydration of anhydrofulvic acid and its derivatives to the corresponding fulvates was effected without difficulty by aqueous mineral acids and was extended to the acid-catalysed addition of alcohols with the production, for example, of methyl tri-*O*-methylfulvate, having an ultraviolet spectrum almost identical with that of methyl di-*O*-methylfulvate but devoid of hydroxylic absorption near 3400 cm.$^{-1}$. When it was also found that the elements of the appropriate alcohol could be removed from the new ethers by sublimation or by treatment with hot acetic acid, the resemblance of these reactions to those characteristic of dihydropyran and other vinyl ethers led to the view that anhydrofulvates contained the grouping $\cdot\underset{|}{C}{:}\underset{|}{C}\cdot O\cdot$, fulvates the grouping $\cdot\underset{|}{C}H\cdot\underset{|}{C}(OH)\cdot O\cdot$, and the new ethers the grouping $\cdot\underset{|}{C}H\cdot\underset{|}{C}(OR)\cdot O\cdot$. It was subsequently discovered that the

[6] Bellamy, "The Infra-red Spectra of Organic Molecules," Methuen, 1954, p. 158.

addition of alcohols to anhydrofulvates was also catalysed by bases. Since simple vinyl ethers are unresponsive to bases, it appeared necessary to develop a formulation permitting conjugation of the vinyl double bond with a carbonyl group as in the system ·CO·C:C·O·. This interpretation was supported by hydrogenation of methyl anhydrodi-*O*-methylfulvate to the dihydro-derivative methyl deoxydi-*O*-methylfulvate, a compound that was inert to aqueous or alcoholic acids or bases and had an ultraviolet absorption spectrum very like that of methyl di-*O*-methylfulvate, facts which could readily be accommodated by the partial structure ·CO·CH·CH·O·. It was obvious that hydrogenation had not affected the carbonyl group because methyl deoxydi-*O*-methylfulvate could not be acetylated and did not have a hydroxyl band in its infrared absorption spectrum.

That methyl anhydrodi-*O*-methylfulvate contained one *C*-methyl group was evident from Kuhn–Roth determinations. This methyl group was clearly "active" since the ester gave a piperonylidene derivative devoid of *C*-methyl groups. Methyl deoxydi-*O*-



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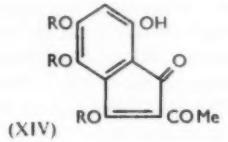

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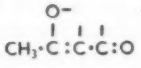
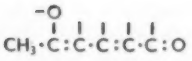


(XV)



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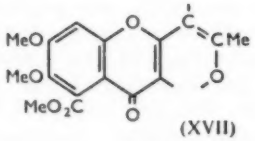

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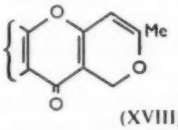
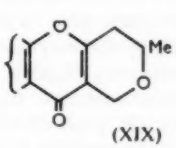


(XVIII)

methylfulvate did not condense with piperonaldehyde and therefore hydrogenation must have destroyed a double bond connecting the methyl group with a carbonyl group. This and the above facts were most neatly incorporated in partial structure (XV) for methyl anhydrodi-*O*-methylfulvate.

In combination, the expressions (XIII; R = Me) and (XV) contain eight oxygen atoms whereas methyl anhydrodi-*O*-methylfulvate contains but seven. In the summation, at least one oxygen atom must therefore be common to both expressions, but identification of either oxygen atom of (XV) with the appropriate atom in (XIII) also necessitated identification of the double bond of (XV) with the 2 : 3-double bond of (XIII). This secondary identification was impossible because chromone double bonds are inert and do not have the properties attributed to that in (XV). It became clear that expression (XV) had to be expanded to the vinylogue (XVI), the combination of which with (XIII) presented no difficulty and gave the partial structure (XVII) for methyl anhydrodi-*O*-methylfulvate. This structure (XVII) differs from a complete structure by one methylene group which could be inserted in two ways, one giving the pyran (XVIII) and the other giving the oxeten (XXI). It has been possible to exclude the latter alternative, and therefore we represent methyl anhydrodi-*O*-methylfulvate by structure (XVIII), fulvic acid by (I; R = H), methyl tri-*O*-methylfulvate by (XX), and methyl deoxydi-*O*-methylfulvate by (XIX). The possibility of ring–chain tautomerism between fulvic acid (I; R = H) and the system (XXII) accounted for the absence of optical activity in spite of the presence of the asymmetric carbon atom starred in (I). The hydrolysis of (XXII) could have proceeded by way of (XXIII) from which the loss of the terminal acetyl group and of the hydroxymethyl group (by a reverse aldol condensation) would result in the triketone (X), but we have not been able to identify formaldehyde as a product of this reaction and have detected but small amounts of formic acid. The polyketone (XXIII) could also suffer

hydrolysis to acetone and acetic acid; these products were easily detected. Oxidation of polyketone (XXIII) or an equivalent clearly accounted for the production of the 4-hydroxycoumarin (V; R = CO_2Me).



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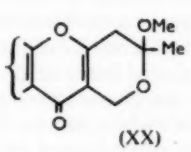
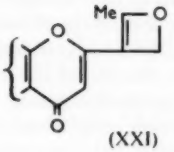
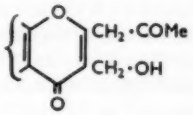


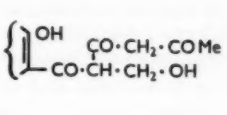
(XX)



(XXI)

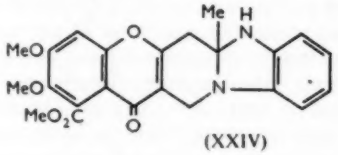
(XXII)



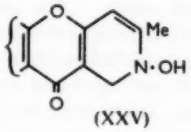


(XXIII)

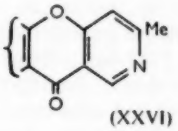
As remarked earlier, derivatives of fulvic acid do not behave as ketones (methyl deoxydi-*O*-methylfulvate was completely inert to carbonyl reagents), but the relation of the fulvates to the system (XXII) would be expected to result in some kind of modified carbonyl activity in this series. This was observed in reactions with *o*-phenylenediamine and hydroxylamine.



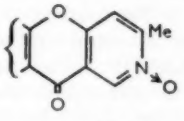
(XXIV)



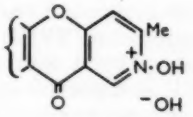
(XXV)



(XXVI)



(XXVII)



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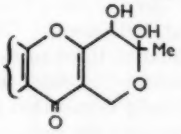

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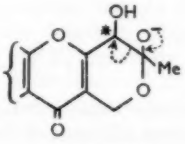

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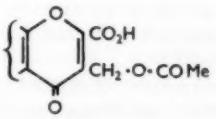
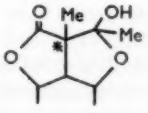
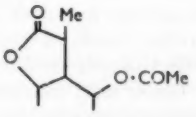


(XXXI)



(XXXII)



(XXXIII)

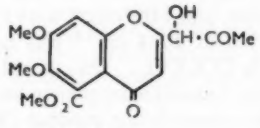
In contrast with the normal α-diketone reaction, interaction of methyl anhydrodi-*O*-methylfulvate (XVIII) and *o*-phenylenediamine was accompanied by elimination of only one mol. of water, but the product could not be diazotised and therefore did not contain a free primary amino-group. This reaction clearly involved the pyran ring only, because the product possessed infrared absorption bands at 1736 cm.$^{-1}$ (methoxycarbonyl), and at 1643, 1609, 1582, and 1479 cm.$^{-1}$ (chromone and benzene rings) and also because of the inertness of methyl deoxydi-*O*-methylfulvate (XIX) towards the same reagent. The anomaly can be explained in terms of structure (XVIII) for methyl anhydrodi-*O*-methylfulvate because replacement of the pyran oxygen atom by one nitrogen atom would permit the free amino-group to add to the active double bond after the fashion of water and alcohols. Consequently the product is considered to have structure (XXIV).

With hydroxylamine, methyl anhydrodi-*O*-methylfulvate (XVIII) underwent a complex reaction from which only a small quantity of a coherent product could be isolated. Much importance was attached to this compound because it seemed that the replacement of the pyran oxygen atom by a hydroxyamino-residue would give an intermediate (XXV) from which loss of the elements of water could yield the pyridine derivative (XXVI) by a simple variation of Knoevenagel's modification [7] of the Hantzsch pyridine synthesis, thus establishing the size of the terminal ring of fulvic acid. This pyridine $C_{17}H_{15}O_6N$ (XXVI), if formed, escaped isolation because the characterised product gave analytical data which accorded much more closely with the hydroxylamine derivative $C_{17}H_{17}O_7N$ (XXV). The data, however, fitted precisely a compound having the empirical composition $C_{17}H_{15}O_7N$, thus suggesting that the hydroxylamine derivative (XXV) has suffered oxidation to the pyridine oxide (XXVII), a formulation supported by the properties of the compound and by the discussions presented by Rogers,[8] which show that dialkylhydroxylamines readily undergo autoxidation to nitrones and other substances equivalent to the pyridine oxide (XXVII) under conditions similar to those obtaining in the preparation of this substance. In common with amine oxides,[9] the hydroxylamine condensation product liberated iodine from hydrogen iodide and was insoluble in alkaline media. It was, however, very weakly basic and dissolved only in relatively concentrated mineral acids, a behaviour which was not surprising because amine oxides are considerably weaker bases [9] than their parent amines, and, in addition, the present example was in effect derived from a 3-acylpyridine similar to 3-acetylpyridine which is a much weaker base [10] than pyridine. This low basicity also accounted for the apparent inability of the compound to form a hydrate (XXVIII) of the type usually formed by amine oxides. The infrared absorption spectrum of the compound was, as expected, devoid of hydroxyl or imino-stretching frequencies and showed a peak at 1752 cm.$^{-1}$ due to the methoxycarbonyl group; the chromone pattern was no longer evident. An important new band had appeared at 1664 cm.$^{-1}$, indicating that the pyran ring had aromatised, since frequencies in this region are typical of many of the more complex derivatives of benzophenone—in particular, 4-methoxyxanthone was found to absorb at 1661 cm.$^{-1}$. The ultraviolet and visible spectra of the condensation product were similar to those of the parent ester (XVIII) and to those of several xanthones [11] and were therefore at least not inconsistent with structure (XXVII). This interpretation automatically eliminated (XXI) as a possible structure for methyl anhydrodi-*O*-methylfulvate because the corresponding amine oxide would have had two double bonds in a four-membered ring and therefore be prohibitively strained; but the oxeten (XXI) might have reverted to a β-hydroxy-ketone from which condensation with hydroxylamine and loss of two hydrogen atoms could have produced an *iso*oxazole easily confused with a pyridine oxide of type (XXVII). Independent evidence against structure (XXI) for methyl anhydrodi-*O*-methylfulvate was sought.

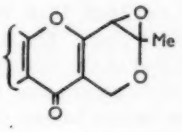
Under mild conditions, permanganate oxidation of methyl anhydrodi-*O*-methylfulvate resulted in an acid devoid of carbonyl activity and formed simply by the addition of three oxygen atoms to the original ester, thus eliminating structure (XXI) which offered opportunity only for the formation of a neutral acetoxy-ketone by fission of the double bond in the four-membered ring. With diazomethane, this acid gave an ester containing four methoxyl groups and having the intense absorption near 1730 cm.$^{-1}$ expected from a polyester. The infrared absorption spectrum of the ester and the ultraviolet spectrum of the acid indicated that the chromone ring was intact, but peaks indicative of new carbonyl or hydroxyl groups were not present. Having regard to the course usually taken by permanganate oxidations, we considered the primary oxidation product to be the glycol

[7] Knoevenagel, *Annalen*, 1894, **281**, 25.
[8] Rogers, *J.*, 1956, 2784.
[9] Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[10] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.
[11] Lund, Ph.D. Thesis, Liverpool, 1952.

(XXIX), further oxidation of which appeared to be governed by the basicity of the reaction mixture, since this acid was never obtained when magnesium sulphate was included. Removal of a proton from the glycol (XXIX) to give an ion (XXX), in which electrons could move (as indicated) towards the starred carbon atom and be there stabilised by conjugation with the chromone carbonyl group, would result in a system that would subsequently be oxidised to the acid (XXXI). This mode of fission is virtually the same as that recently considered by Barton and de Mayo,[12] and by Braun, Herz, and Rabindran,[13] to account for the base-catalysed isomerisation of tenulin, partial structure (XXXII), to *iso*tenulin, partial structure (XXXIII). The structure (XXXI) agreed excellently with the properties of the acid given above and also with the isolation of approximately one mol. of volatile acid after acidic hydrolysis (chromone rings are generally stable in the conditions employed) as opposed to the neutralisation of three equivalents of base in alkaline hydrolysis. The absence of a 2-methylchromone system in the acid was clear from the negative Zimmermann reaction.[14]



(XXXIV)



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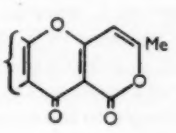
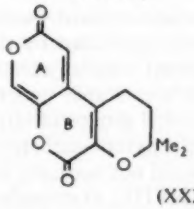
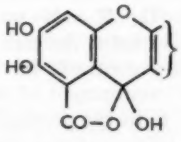


(XXXVI)



(XXXVII)



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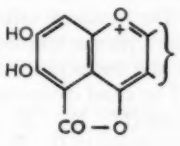
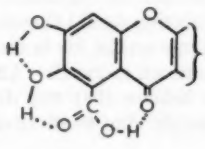
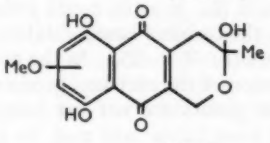


(XXXIX)



(XL)



(XLI)

With osmium tetroxide, methyl anhydrodi-*O*-methylfulvate formed an intractable adduct. Although methyl deoxydi-*O*-methylfulvate (XIX) was inert, the anhydrofulvate (XVIII) rapidly destroyed one equivalent of perbenzoic acid and then suffered a further, slower oxidation. From the very variable reaction mixture, it was occasionally possible to isolate small quantities of an interesting crystalline product. The derivative which this compound rapidly formed with 2 : 4-dinitrophenylhydrazine unfortunately resinified, but the infrared absorption spectrum revealed a new unconjugated carbonyl group (peak at 1724 cm.$^{-1}$) and also a new hydroxyl group (peak near 3400 cm.$^{-1}$). Bands at 1745, 1647, and 1608 cm.$^{-1}$ attested the survival of the methoxycarbonyl and chromone systems. Taken in conjunction with the molecular formula $C_{16}H_{16}O_8$ and the stability of the substance to dilute acids, these facts enabled structure (XXXIV) to be allocated to the ketonic oxidation product. Whilst the ketone (XXXIV) was insoluble in aqueous sodium hydrogen carbonate, it dissolved in and was rapidly decomposed by aqueous sodium

[12] Barton and de Mayo, *J.*, 1956, 142.
[13] Braun, Herz, and Rabindran, *J. Amer. Chem. Soc.*, 1956, **78**, 4423.
[14] Schönberg and Sidky, *J. Org. Chem.*, 1956, **21**, 476.

XUM

hydroxide, an observation which was not thought to invalidate structure (XXXIV) because the negative ferric reaction excluded the possibility that a phenolic or enolic hydroxyl group was present and also because a similar compound [(XXXIV) less the hydroxyl group] obtained from citromycetin behaved in the same way. On the other hand, there is no evidence as to the way in which the methylene group is lost during the formation of (XXXIV) in spite of the fact that the α-ketol system had an obvious origin in the epoxide (XXXV).

Ozonolysis of methyl anhydrodi-*O*-methylfulvate (XVIII) did not gave a tractable product and was of no interest except in that no volatile carbonyl compounds resulted. Oxidation of this ester with lead tetra-acetate or selenium dioxide also gave negative results. Chromic acid oxidation was not satisfactory but gave small quantities of a neutral product $C_{17}H_{14}O_8$ considered to have structure (XXVI) because of the analogy with the chromic acid oxidation of methyl di-*O*-methylcitromycetin (II; R = Me) to the corresponding citromycetinone (VI). In confirmation of this view, the new compound did not react with 2 : 4-dinitrophenylhydrazine and was transparent in the hydroxyl stretching region, whereas peaks at 1643, 1614, 1600, 1553, and 1468 cm.$^{-1}$ were consistent with the presence of a chromone ring. The absorption at 1754 cm.$^{-1}$ was noticeably intensified and clearly included that of the lactone ring in (XXXVI). On general grounds, this type of lactone was expected to absorb near 1745 cm.$^{-1}$ and this frequency has already been attributed to the somewhat similar lactone ring A in a degradation product (XXXVII) of fuscin.[15]

In conclusion, reference must be made to the decarboxylation and infrared spectrum of fulvic acid. The study of citromycetin (II; R = H) was greatly facilitated by the ease with which hot aqueous mineral acids eliminated the carboxyl group without affecting the remainder of the molecule but, in sharp contrast, fulvic acid was stable under these conditions. The chief difference in the environment of the carboxyl groups of structures (I; R = H) and (II; R = H) appeared to be the proximity of the pyrone-carbonyl group to the carboxyl group in (I; R = H). Although these groups would not normally interact with the formation of the lactol having the partial structure (XXXVIII), in strongly acidic media fulvic acid (I; R = H) could yield the oxonium ion (XXXIX) of which the lactol (XXXVIII) is the carbinol base; dilution of the solution would therefore regenerate fulvic acid of structure (I; R = H). As the positive charge on the ion is dispersed, its ability to promote extrusion of the carboxyl group would be much reduced. Although our investigations on these points are not yet complete we believe that the difficulty of isolating oxonium salts from fulvic acid may be at least partly due to disadvantageous solubility relations.

The infrared absorption spectrum of fulvic acid (and of anhydrofulvic acid) was curious in that carbonyl stretching frequencies did not occur above 1645 cm.$^{-1}$. Thus there was no band which could be specifically attributed to the carboxyl group and, in addition, the absorption due to the chromone-carbonyl group had been shifted to longer wavelengths. When fulvic acid was written as in (XL) it became obvious that the conditions for strong hydrogen-bonding were particularly favourable and would result in a spectrum of the observed type.

The structural connections between fulvic acid (I), citromycetin (II; R = H), and fusarubin (XLI) have been discussed elsewhere,[16] and related synthetical investigations will be published separately.

Experimental

Fulvic Acid (I; R = H).—(*a*) *Carpenteles brefeldianum* Dodge (Shear) (L.S.H.T.M. Catalogue No. P157) was incubated on Raulin–Thom medium in the manner described by Oxford, Raistrick,

[15] Barton and Hendrickson, *J.*, 1956, 1028.
[16] Dean, Eade, Moubasher, and Robertson, *Nature*, 1957, **179**, 366.

XUM

and Simonart,[1] except that a somewhat higher temperature (26°) was used to allow the isolation of satisfactory yields of fulvic acid from the culture medium after an appreciably shorter period (28 days) of growth. Obtained by acidification of the culture fluid, the crude acidic pigment was completely soluble in aqueous sodium hydrogen carbonate and so the corresponding part of the original purification procedure was omitted in favour of extraction with ethyl acetate in which fulvic acid dissolved, leaving a residue which has not yet been examined closely. Further purification was effected by repeated crystallisation from anhydrous instead of aqueous dioxan and gave fulvic acid in pale yellow prisms, m. p. 244° (vigorous decomp.), which became brown and softened above 200° (Found, on a sample dried for 8 hr. at 110° *in vacuo*: C, 54·4; H, 4·1. Calc. for $C_{14}H_{12}O_8$: C, 54·6; H, 3·9%) [Oxford *et al.*[1] give m. p. 246° (decomp.)]. In alcohol, fulvic acid gave a deep green ferric reaction and had $\lambda_{max.}$ 225, 318, and 343 mμ (log ε 4·47, 4·07, 4·05). This acid had infrared bands at 3550 (sharp; free OH), 3540—2500 (broad; ill-defined; bonded OH), 1645, 1567, 1497, 1420, 1362, 1340, 1290, 1256, 1222, 1172 (broad), 1121, 1092, 1062, 975, 950, 926 (broad), 877, 855, 820, 807, 769, and 763 cm.$^{-1}$. Fulvic acid (0·15 g.) was recovered when its bright yellow solution in sulphuric acid monohydrate (15 ml.) was kept overnight and then poured on ice.

(*b*) Anhydrofulvic acid (0·2 g.) was heated under reflux with 2N-aqueous sulphuric acid (50 ml.). After 1 hr. the cooled solution was diluted to precipitate fulvic acid, which formed prisms (0·13 g.), m. p. and mixed m. p. 244° (decomp.), from dioxan; identification was effected spectroscopically. A similar experiment was conducted under nitrogen for 12 hr.; a little carbon dioxide was evolved and was detected by means of barium hydroxide but the only crystalline product was again fulvic acid.

Alkaline Degradation of Fulvic Acid.—(a) *Acetone and acetic acid.* A mixture of fulvic acid (1·5 g.) and 2N-aqueous sodium hydroxide was slowly distilled during ½ hr., with the addition of water to maintain the original volume. The distillate yielded acetone 2 : 4-dinitrophenylhydrazone which was purified by chromatography from light petroleum (b. p. 60—80°) on a column of aluminium oxide and then crystallised from aqueous alcohol, forming yellow needles, m. p. and mixed m. p. 124—125°.

Acidification of the residual alkaline liquor gave a yellow-brown amorphous precipitate which was removed. Distillation of the filtrate gave 0·94 equivalent of volatile acids including acetic acid, which was identified as 2-methylbenziminazole, m. p. and mixed m. p. 173—174°.

(b) *Carbon dioxide.* Fulvic acid (2·05 g.) was heated under reflux with 10% aqueous sodium hydroxide (30 ml.) in nitrogen for ½ hr. The cooled mixture was acidified carefully with 2N-sulphuric acid and then warmed gently during the passage of a slow stream of nitrogen from the mixture into standardised barium hydroxide solution. Titration of the unchanged alkali showed that 0·812 mol. of carbon dioxide had been produced. In similar experiments with anhydrofulvic acid, 0·850 mol. of carbon dioxide was produced, but methyl anhydrodi-*O*-methylfulvate gave negligible quantities of this gas.

Methyl Di-O-methylfulvate (I; R = Me).—(*a*) Methylation of fulvic acid with diazomethane or with methyl sulphate and sodium carbonate as described by Oxford *et al.*[1] gave methyl di-*O*-methylfulvate (I; R = Me), crystallising from aqueous dioxan in prisms, m. p. 186—187° (decomp.) (the previous authors quote m. p. 186—188°) (Found: C, 58·4, 58·4; H, 5·1, 5·0. Calc. for $C_{17}H_{18}O_8$: C, 58·3; H, 5·2%). This compound had $\lambda_{max.}$ 230, 282, and 300 mμ (log ε 4·41, 4·08, 3·99) with an inflection at 248 mμ (log ε 4·04). Infrared absorption occurred at 3448 (OH), 3050 (aromatic CH), 1742 (CO_2Me), 1647, 1592, 1550, 1420, 1400, 1312, 1274, 1258, 1235, 1205, 1171, 1153, 1111, 1039. 1022, 1010, 994, 953, 884, 866, 840, 813, 800, and 726 cm.$^{-1}$. This ester was insoluble in dilute sodium hydroxide and gave no ferric reaction.

(*b*) The solution obtained by heating methyl anhydrodi-*O*-methylfulvate (1·0 g.) for ¾ hr. with methanol (20 ml.) and 2N-sulphuric acid (20 ml.) was diluted with water (40 ml.) and concentrated under reduced pressure to 35 ml. in order to precipitate unchanged methyl anhydrodi-*O*-methylfulvate (0·1 g.). On being kept, the filtrate deposited methyl di-*O*-methylfulvate in prisms (0·85 g.), m. p. and mixed m. p. 191° (decomp.). This ester was not very soluble in dioxan or water but dissolved readily in mixtures of the two solvents.

Methyl Tri-O-methylfulvate (XX).—(*a*) Methanol (5 ml.) containing sodium methoxide (from 0·2 g. of sodium) was added to methyl anhydrodi-*O*-methylfulvate (1·0 g.) suspended in warm absolute methanol (10 ml.) which soon cleared, then became green, and finally brown. In a few days *methyl tri-O-methylfulvate* (XX) separated and was purified from benzene–light petroleum (b. p. 40—60°), forming cubes, m. p. 176—177° (decomp.), devoid of a ferric reaction

[Found, in specimen dried for 3 hr. at 80° *in vacuo*: C, 59·3; H, 5·8; OMe, 32·6. $C_{14}H_8O_4(OMe)_4$ requires C, 59·3; H, 5·5; OMe, 34·1%].

(*b*) From a 3% solution (50 ml.) of hydrogen chloride in absolute methanol containing methyl anhydrodi-*O*-methylfulvate (1·0 g.) a crystalline precipitate (0·8 g.) separated during 2 days. Purified from methanol, this solid gave methyl tri-*O*-methylfulvate (XX) in prisms, m. p. and mixed m. p. 175—176° (decomp.), readily soluble in chloroform and acetone, and having $\lambda_{max.}$ 230, 283, and 300 mμ (log ε 4·42, 4·09, 4·01) with an inflection at 248 mμ (log ε 4·06).

Methyl O-*Ethyldi*-O-*methylfulvate*.—This *ethyl ether* resulted when alcohol was substituted for methanol in the preceding preparations (*a*) and (*b*) and crystallised from alcohol in irregular plates, m. p. 208—209° (decomp.) (Found: C, 60·2, 60·3; H, 5·7, 5·8. $C_{19}H_{22}O_8$ requires C, 60·3; H, 5·9%).

Anhydrofulvic Acid (XVIII; OH for OMe).—When a solution of fulvic acid (8·0 g.) in 70% acetic acid (1 l.) was boiled for 10 min. and cooled, anhydrofulvic acid separated in long yellow crystals (6·4 g.) and on recrystallisation formed rods (from aqueous dioxan) or flat parallelepipeds (from the anhydrous solvent), m. p. 245—246° (after darkening near 235°) [Found, in sample dried to constant weight in a vacuum at 100°: C, 58·1; H, 3·6; *C*-Me (Kuhn–Roth), 5·4. Calc. for $C_{14}H_{10}O_7$: C, 57·9; H, 3·5; *C*-Me, 5·2%] (Oxford *et al.* give m. p. 242—243°). Anhydrofulvic acid (1·0 g.) was not hydrated when boiled for 4 hr. in dioxan (30 ml.) containing water (10 ml.). In alcohol it gave a deep green ferric reaction and had $\lambda_{max.}$ 233, 341, and 387 mμ (log ε 4·28, 4·03, 4·34). Because of the general similarity of this compound to fulvic acid and in particular the absence of noticeable m. p. depression in their mixtures, this compound was invariably characterised by its infrared spectrum: 3200 (bonded OH), 1639, 1623, 1587, 1562, 15·48, 1502, 1404, 1282, 1271, 1205, 1182, 1114, 1042, 990, 978, 914, 815, and 781 cm.$^{-1}$.

Methyl Anhydrodi-O-*methylfulvate* (XVIII).—(*a*) During the vigorous reaction between finely divided anhydrofulvic acid (10 g.), suspended in ether (200 ml.) containing methanol (20 ml.), and ethereal diazomethane [from nitrosomethylurea (30 g.)] the original yellow solid was replaced by buff-coloured solid which was collected next day and purified from methanol, giving *methyl anhydrodi*-O-*methylfulvate* in faintly yellow prisms (9·8 g.), m. p. 193—194° (decomp.), unchanged on sublimation but depressed to 170° on admixture with methyl di-*O*-methylfulvate [Found: C, 61·6, 61·5; H, 4·7, 5·0; OMe, 26·7%; *M* (micro-Rast), 324. $C_{14}H_7O_4(OMe)_3$ requires C, 61·4; H, 4·9; OMe, 28·0%; *M*, 332]. This compound was much more soluble in chloroform, hot benzene, or acetone than in methanol or ethyl acetate, and was unaffected by boiling dioxan (20 ml.) containing water (5 ml.) during 6 hr. It had $\lambda_{max.}$ 235, 257, 318, and 348 mμ (log ε 4·12, 4·09, 4·13, 4·20) and infrared bands at 3050 (aromatic and olefinic CH), 1751 (CO_2Me), 1647, 1597, 1562, 1425, 1403, 1314, 1277, 1258, 1133, 1203, 1190, 1163, 1153, 1110, 1042, 1024, 1012, 996, 990, 953, 878, 866, 839, 810, 799, 789, 751, and 727 cm.$^{-1}$.

(*b*) The mixture obtained by the addition of methyl sulphate (60 ml.) in methanol (30 ml.) to a stirred solution of anhydrofulvic acid (10 g.) in N-aqueous sodium carbonate (200 ml.) was treated gradually with 2N-aqueous sodium carbonate (400 ml.) so as to maintain slight alkalinity; the temperature was not allowed to rise above 40°. After 2 hr., the solid was collected, triturated with dilute aqueous sodium hydroxide, and purified from methanol, giving methyl anhydrodi-*O*-methylfulvate in prisms (9·3 g.), m. p. 193°, not depressed by admixture with a specimen from (*a*) (Found: C, 61·3; H, 4·7%). Acidification of the alkaline liquors gave a slight precipitate partly soluble in aqueous sodium hydrogen carbonate. Regained from this solution and crystallised from aqueous methanol, this acidic fraction supplied *anhydrodi*-O-*methylfulvic acid* (XVIII; CO_2H for CO_2Me) in pale yellow plates (0·1 g.), m. p. 219—220° (decomp.) (Found, on specimen dried *in vacuo* at 120° for 8 hr.: C, 60·0; H, 4·6%; equiv., 306. $C_{15}H_{12}O_8 \cdot CO_2H$ requires C, 60·4; H, 4·4%; equiv., 318).

(*c*) When sublimed at 180°/0·005 mm., methyl di-*O*-methyl-, methyl tri-*O*-methyl-, or methyl *O*-ethyldi-*O*-methyl-fulvate gave methyl anhydrodi-*O*-methyl-fulvate, m. p. and mixed m. p. 193° (decomp.).

(*d*) Kept in boiling acetic acid (5 ml.) for 10 min., methyl di-*O*-methyl- (0·5 g.), methyl tri-*O*-methyl- (0·5 g.), or methyl *O*-ethyldi-*O*-methyl-fulvate (0·5 g.) gave methyl anhydrodi-*O*-methylfulvate which was precipitated with water and had m. p. and mixed m. p. 193° after purification from methanol (yield, 0·42 g.).

Interaction of methyl anhydrodi-*O*-methylfulvate (0·5 g.) and piperonaldehyde (0·5 g.) in warm methanol (20 ml.) containing sodium methoxide (from 0·2 g. of sodium) for 10 min. gave

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the *piperonylidene derivative* (0·4 g.) which separated from the mixture in two weeks and then formed long orange needles, m. p. 217—218° (decomp.), from methanol [Found, on specimen dried for 3 hr. in a vacuum at 80° : C, 64·8; H, 4·4; *C*-Me (Kuhn–Roth), 0. $C_{25}H_{20}O_9$ requires C, 64·7; H, 4·3%].

Ethyl Anhydrodi-O-ethylfulvate (XVIII; OEt for OMe).—Prepared from anhydrofulvic acid (1·0 g.) as in (*a*) above, but by using diazoethane instead of diazomethane, *ethyl anhydrodi-O-ethylfulvate* was freed from traces of phenolic material by means of cold dilute sodium hydroxide and then crystallised from alcohol, forming yellow plates (0·5 g.), m. p. 149—151° (decomp.) [Found, on specimen dried for 3 hr. at 80° *in vacuo* : C, 64·1, 64·0; H, 5·6, 6·0; OEt, 33·0. $C_{14}H_7O_4(OEt)_3$ requires C, 64·2; H, 5·9; OEt, 36·1%].

Methyl Deoxydi-O-methylfulvate (XIX).—Shaken with 10% palladium–charcoal (3 g.) a solution of methyl anhydrodi-*O*-methylfulvate (3 g.) in ethyl acetate (250 ml.) absorbed hydrogen (240—270 ml. Calc. for 1 mol. : 215 ml.). Concentration of the filtrate to 50 ml. induced the separation of *methyl deoxydi-O-methylfulvate* which formed prisms (2·3 g.), m. p. 199—200° (from ethyl acetate), with a negative ferric reaction [Found, on specimen dried for 3 hr. at 100° *in vacuo* : C, 61·1, 61·0, 61·3, 61·0; H, 5·4, 5·6, 5·3; OMe, 27·3, 27·3, 27·5, 27·2. $C_{14}H_8O_4(OMe)_2$ requires C, 61·1; H, 5·4; OMe, 27·8%]. This ester, which had $\lambda_{max.}$ 230, 282, and 303 mμ (log ε 4·40, 4·08, 4·00) and infrared absorption at 1740 (CO_2Me), 1647 (chromone C:O), 1623, 1603, and 1580 (shoulder) cm.$^{-1}$, was insoluble in dilute aqueous sodium hydroxide, and did not react under a wide variety of conditions with 2 : 4-dinitrophenylhydrazine, hydroxylamine, *o*-phenylenediamine, or piperonaldehyde. When kept in dioxan containing an equal volume of 2N-aqueous sulphuric acid at 100° for 1 hr. it was recovered unchanged, and it resisted the action of boiling acetic anhydride containing sodium acetate for 1 hr.

The residue from evaporation of the mother-liquors of methyl deoxydi-*O*-methylfulvate was purified by chromatography from benzene on aluminium oxide, giving a *compound* which separated from benzene–light petroleum (b. p. 60—80°) in irregular prisms (0·16 g.), m. p. 180—181° (Found : C, 60·8, 61·0; H, 5·8, 5·9. $C_{17}H_{10}O_7$ requires C, 60·7; H, 6·0%). Elution of the column with 1 : 9 acetone–benzene gave methyl anhydrodi-*O*-methylfulvate (0·14 g.), m. p. and mixed m. p. 197—198°.

Condensation of Methyl Anhydrodi-O-methylfulvate with o-Phenylenediamine. Methyl 1 : 2 : 3 : 4 : 9 : 10-Hexahydro-6 : 7-dimethoxy-2-methyl-10-oxo-9-oxa-3 : 1′-diazaindeno(2′ : 3′-2 : 3)-anthracene-5-carboxylate (XXIV).—A mixture of methyl anhydrodi-*O*-methylfulvate (0·5 g.) and *o*-phenylenediamine (0·5 g.) in alcohol (8 ml.) containing acetic acid (1 ml.) was heated under reflux for 1 hr. Addition of water (20 ml.) to the cold solution produced a turbidity that was cleared by charcoal, whereupon neutralisation of the filtrate gave a cream precipitate (0·6 g.) which, on crystallisation from alcohol, gave the *oxadiazaindenoanthracene* (XXIV) in prisms, m. p. 209—211° after being dried at 100° *in vacuo* [Found : C, 64·6, 64·1; H, 5·4, 4·9; N, 6·1; OMe, 22·8. $C_{20}H_{13}O_3N_2(OMe)_3$ requires C, 65·4; H, 5·3; N, 6·6; OMe, 22·0%]. This compound was readily soluble in dilute acids but gave only a yellow colour on treatment with nitrous acid followed by alkaline β-naphthol. The *picrate* separated from an alcoholic mixture and on purification from acetic acid formed plates, m. p. 263° (decomp.) (Found, on specimen dried for 2 hr. at 120° *in vacuo* : C, 53·9; H, 3·8; N, 10·5, 10·6. $C_{29}H_{25}O_{13}N_5$ requires C, 53·5; H, 3·9; N, 10·8%).

Methyl 6 : 7-Dimethoxy-6′-methylpyridino(4′ : 3′-2 : 3)chromone-5-carboxylate 1′-Oxide (XXVII).—Methyl anhydrodi-*O*-methylfulvate (1·0 g.) was heated with hydroxylamine hydrochloride (0·65 g.) and hydrated sodium acetate (1·4 g.) in boiling methanol (20 ml.) for 1 hr. and the dark yellow filtered mixture was concentrated to 10 ml., diluted with water (10 ml.), and kept in air for several days. The resulting semi-crystalline mass (0·15 g.) was repeatedly purified from alcohol, giving the *pyridine oxide* (XXVII) in small yellow prisms, m. p. 266° (decomp.), insoluble in dilute aqueous sodium hydroxide and 2N-hydrochloric acid, but soluble in 10N-hydrochloric acid (Found : C, 59·1, 59·1; H, 4·5, 4·1; N, 4·0. $C_{17}H_{15}O_7N$ requires C, 59·1; H, 4·4; N, 4·1%). This compound did not give a ferric reaction but under conditions in which methyl anhydrodi-*O*-methylfulvate was inert it liberated iodine from hydrogen iodide, identified on extraction into chloroform and subsequently into aqueous potassium iodide by the usual characteristic tests with starch and thiosulphate. The pyridine oxide had $\lambda_{max.}$ 242, 282, and 326 mμ (log ε 4·08, 4·49, 4·38) and infrared bands at 3040 (aromatic CH), 1752 (CO_2Me), 1664 (conjugated C:O), 1633, 1609, 1435, 1418, 1335, 1311, 1285, 1228, 1180, 1095, 1020, 1012, 982, 962, 935, 894, 856, 799, 788, and 758 cm.$^{-1}$.

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Alkaline Degradation of Methyl Anhydrodi-O-methylfulvate. 2-Acetyl-7-hydroxy-4 : 5-dimethoxyindane-1 : 3-dione (X).—When a stream of nitrogen was led through a solution of methyl anhydrodi-*O*-methylfulvate (3·32 g.) in boiling dioxan or methanol (10 ml.) containing 2N-aqueous sodium hydroxide (80 ml.) for ¾ hr. the effluent gases gave negative tests for carbonyl compounds. On being kept at 0° for 8 hr. the brown solution deposited a yellow sodium salt (0·5 g.) and acidification of the filtrate from this gave a brown solid which with warm 2N-aqueous sodium hydroxide (20 ml.) yielded a further quantity (1·1 g.) of the yellow salt. Decomposed by acids, the sodium salts furnished the 2-acetyl-7-hydroxy-4 : 5-dimethoxyindane-1 : 3-dione (X) in pale yellow needles (1·2 g.), m. p. 157°, having a purple-brown ferric reaction in methanol [Found, on a specimen sublimed at 150°/0·01 mm. : C, 59·2; H, 4·5; OMe, 23·6. Calc. for $C_{11}H_6O_4(OMe)_2$: C, 59·1; H, 4·6; OMe, 23·5%]. Admixed with the so-called 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid prepared from citromycetin this had m. p. 157°; the two specimens had identical ultraviolet and infrared absorption spectra : $\lambda_{max.}$ 300 mμ (log ε 4·52); infrared bands at 3400 (phenolic OH), 1704, 1645, 1605, 1572 (shoulder), 1508, 1408, 1330, 1302, 1280, 1221, 1197, 1138, 1133, 1007, 945, 926, 907, 897, 845, 832, and 815 cm.$^{-1}$. The oxime separated from alcohol in small yellow needles, m. p. 213—214°, unchanged on admixture with the derivative from citromycetin (Found : C, 55·5, 55·5; H, 4·6, 4·8; N, 4·6. Calc. for $C_{13}H_{13}O_6N$: C, 55·9; H, 4·7; N, 5·0%). On methylation with methyl iodide (5 ml.) and potassium carbonate (1·5 g.) in boiling acetone (50 ml.) the indanedione gave a red gum which was purified from benzene with aluminium oxide and then extracted repeatedly with boiling light petroleum. The extract gradually crystallised and then on purification from the same solvent gave the *dimethyl ether* in needles, m. p. 77°, insoluble in aqueous sodium hydroxide and having a negative ferric reaction [Found : C, 61·2; H, 5·7; OMe, 43·0. $C_{13}H_{10}O_4(OMe)_4$ requires C, 61·6; H, 5·5; OMe, 42·5%].

After removal of the indanedione, the acidified hydrolysate was distilled almost to dryness to recover the volatile acids (1·07 mol. by titration). After treatment of the distillate with potassium permanganate and destruction of the excess of the oxidant by hydrogen peroxide and dilute sulphuric acid, re-distillation afforded volatile acid (1·03 ml.), identified as acetic acid by conversion into 2-methylbenziminazole, m. p. and mixed m. p. 175—176°, and into acetanilide, m. p. and mixed m. p. 112°.

Ozonolysis of Methyl Anhydrodi-O-methylfulvate.—A stream of ozone and oxygen was passed through a solution of methyl anhydrodi-*O*-methylfulvate (1·0 g.) in chloroform (40 ml.) cooled in ice-salt until ozone was no longer absorbed (½ hr.). The residue left on evaporation was treated with water (50 ml.) and, next day, the mixture was heated on the steam-bath for ½ hr., giving a cream solid which did not crystallise. With aqueous 2 : 4-dinitrophenylhydrazine sulphate the solution gave an amorphous precipitate which was still amorphous after purification from benzene on a column of aluminium oxide; a sample of the solution was distilled but the distillate did not give a precipitate with this reagent. In another experiment the distillate from the reaction mixture contained 0·3 equivalent of volatile acids, but the dried sodium salts of these failed to give a crystalline derivative with *o*-phenylenediamine hydrochloride.

Methyl 6 : 7-Dimethoxy-6′-methyl-α-pyrono(4′ : 3′-2 : 3)chromone-5-carboxylate (XXXVI).—Obtained by the dropwise addition of chromic oxide (1·4 g.) in 80% acetic acid (10 ml.) at 50° during 1 hr., the mixture was kept for an hour at the same temperature. Next day, the solution was evaporated, the residue was stirred with water and extracted with chloroform (8 × 15 ml.), the extract was washed with N-aqueous sodium hydroxide, N-hydrochloric acid, and water, dried (Na_2SO_4), and evaporated, and the product extracted with boiling benzene to remove methyl anhydrodi-*O*-methylfulvate (0·8 g.). The residual solid was purified from alcohol, giving the *α-pyronochromone* (XXXVI) in pale cream plates (110 mg.), m. p. 250° (decomp.), inert towards ferric chloride and 2 : 4-dinitrophenylhydrazine sulphate [Found : C, 59·4; H, 4·1; OMe, 25·5. $C_{14}H_8O_6(OMe)_2$ requires C, 59·0; H, 4·1; OMe, 26·9%].

Oxidation of Methyl Anhydrodi-O-methylfulvate with Potassium Permanganate.—(a) *6-Hydroxy-3 : 4-dimethoxy-2-methoxycarbonylbenzoic acid* (III) *and methyl 4-hydroxy-6 : 7-dimethoxycoumarin-5-carboxylate* (V; R = CO_2Me). To methyl anhydrodi-*O*-methylfulvate (2·5 g.) in boiling acetone (200 ml.) potassium permanganate (9 g.) was added during 2 hr. and 15 min. later the mixture was cleared by means of water (100 ml.) and sulphur dioxide and concentrated under reduced pressure to *ca.* 120 ml. The products were extracted with ether (8 × 50 ml.) and washed with water, and the acids were separated with aqueous sodium hydrogen carbonate (2 × 25 ml.) from a neutral non-ketonic substance which formed prisms (30 mg.), m. p. 206°

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(decomp.), from methanol (Found : C, 53·8; H, 4·2%). Liberated by dilute hydrochloric acid and isolated by ether, the acidic fraction formed a gum (1·2 g.) partly soluble in boiling benzene (2 × 10 ml.). Crystallised from aqueous dioxan the residue, insoluble in benzene, gave *methyl 4-hydroxy-6 : 7-dimethoxycoumarin-5-carboxylate* in long cream prisms (0·1 g.), m. p. 255—256° (decomp.), having a brownish ferric reaction but soluble in sodium hydrogen carbonate solutions and devoid of carbonyl activity [Found, in a specimen dried for 7 hr. at 110° *in vacuo* : C, 55·5; H, 4·3; OMe, 34·1, 32·9. $C_{10}H_3O_4(OMe)_3$ requires C, 55·7; H, 4·3; OMe, 33·2%].

When the concentrated benzene extract was kept 6-hydroxy-3 : 4-dimethoxy-2-methoxycarbonylbenzoic acid (III) separated and on recrystallisation from benzene formed prisms (0·7 g.), m. p. 147—148°, unaffected on admixture with a sample prepared from citromycetin [Found : C, 51·8; H, 4·6; OMe, 36·4. Calc. for $C_8H_3O_4(OMe)_3$: C, 51·6; H, 4·7; OMe, 36·3%]. This acid was characterised by its conversion [4] into 6-ethoxy-3 : 4-dimethoxyphthalic anhydride (IV), m. p. 195°, identical with a specimen prepared by the method of Mackenzie and Robertson [3] (Found : C, 57·5; H, 5·0. Calc. for $C_{12}H_{12}O_6$: C, 57·1; H, 4·8%).

(b) *3-Acetoxymethyl-6 : 7-dimethoxy-5-methoxycarbonylchromone-2-carboxylic Acid* (XXXI).—Powdered potassium permanganate (2·0 g.) was added to a solution of methyl anhydrodi-*O*-methylfulvate (2·0 g.) in acetone (200 ml.) at 0° during 5 hr. and, after clarification with water (100 ml.) and sulphur dioxide, the mixture was concentrated under reduced pressure at below 40°, and extracted with ethyl acetate (6 × 25 ml.). The extracts were washed with water and then dilute sodium hydrogen carbonate (2 × 25 ml.), and evaporated, leaving methyl di-*O*-methylfulvate (0·5 g.), m. p. and mixed m. p. 192° (decomp.). Acidification of the alkaline extract furnished a buff solid (0·55 g.) which was leached with boiling benzene (2 × 10 ml.) and crystallised from aqueous methanol, giving the *acid* (XXXI) in needles, m. p. 233—234° (decomp.), devoid of a ferric reaction and of carbonyl activity towards 2 : 4-dinitrophenylhydrazine sulphate [Found : C, 53·3; H, 4·3; OAc, 10·0%; equiv. (hydrolysis by 0·04N-sodium hydroxide, at 100° for ½ hr., back-titration by 0·01N-hydrochloric acid), 123. $C_{13}H_{13}O_8$·OAc requires C, 53·7; H, 4·2; OAc, 11·3%; equiv. (3 acid functions), 127]. This acid had $\lambda_{max.}$ 221, 314 mμ (log ε 4·39, 3·97), inflections at 235, 292 mμ (log ε 4·35, 3·89), and was readily soluble in aqueous sodium hydrogen carbonate but gave a negative Zimmermann reaction.[14] Suspended in ether, the acid reacted rapidly with diazomethane, to furnish the *methyl ester* which separated from methanol in needles, m. p. 195° [Found : 54·5; H, 4·5; OMe, 29·9. $C_{14}H_6O_8(OMe)_4$ requires C, 54·8; H, 4·6; OMe, 31·4%]. The infrared spectrum of the methyl ester included peaks at 3050, 1730 (broad), 1641, 1605 (shoulder at 1582), and 1479 cm.$^{-1}$.

A careful search failed to reveal the presence of 6-hydroxy-3 : 4-dimethoxy-2-methoxycarbonylbenzoic acid in this oxidation mixture.

(c) Experiment (*b*) above was repeated, except that hydrated magnesium sulphate (0·55 g.) in water (60 ml.) was added before the oxidant. Methyl anhydrodi-*O*-methylfulvate (0·9), m. p. and mixed m. p. 192° (decomp.), was recovered, but the chromone-2-carboxylic acid (XXXI) was not detected, and the oily acidic fraction gave the intense ferric reaction characteristic of the phenolic acid (III) although this could not be obtained pure.

Oxidation of Methyl Anhydrodi-O-methylfulvate with Perbenzoic Acid. Methyl 2-1′-Hydroxyacetonyl-6 : 7-dimethoxychromone-5-carboxylate (XXXIV).—In preliminary experiments, methyl anhydrodi-*O*-methylfulvate destroyed 1·02 mol. of perbenzoic acid in ½ hr., but only 0·38 mol. in the next 3 days. Methyl deoxydi-*O*-methylfulvate was hardly attacked by this reagent.

Methyl anhydrodi-*O*-methylfulvate (0·95 g.) in chloroform (10 ml.) at 0° was allowed to react with perbenzoic acid (1·05 mol.) in the same solvent. After 1 hr., the solution was freed from acidic material with aqueous sodium hydrogen carbonate, washed with water, dried (Na_2SO_4), and evaporated at room temperature. The residue was fractionally crystallised from benzene, giving the *compound* (XXXIV) in faintly yellow feathery needles, m. p. 202—204° (decomp.), $\lambda_{max.}$ 314 mμ (log ε 3·99), with a negative ferric reaction (Found : C, 57·4; H, 4·5. $C_{16}H_{16}O_8$ requires C, 57·1; H, 4·8%). With 2 : 4-dinitrophenylhydrazine sulphate, this ketone gave an orange precipitate which resinified when heated in organic solvents. The ketone was insoluble in aqueous sodium carbonate but dissolved rapidly in dilute aqueous sodium hydroxide although it could not be recovered by acidification of the resulting solution; when heated for 1 hr. with N-sulphuric acid (1 ml.), water (20 ml.), and methanol (20 ml.), the ketone was recovered almost quantitatively by removal of the methanol and refrigeration at 0°.

From the fractionation, there was obtained a very small quantity of a substance which

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crystallised from ethyl acetate in small rods, m. p. 237—238° (decomp.) (Found : C, 54·1, 54·1; H, 4·2, 4·3%).

Spectra.—Ultraviolet spectra were determined in alcohol at concentrations near M × 10^{-3} on a Unicam S.P. 300 spectrophotometer. Infrared spectra were determined in paraffin mulls by means of a Grubb-Parsons double-beam spectrophotometer.

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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696. *Vitexin. Part I.*

By W. H. EVANS, A. MCGOOKIN, L. JURD, ALEXANDER ROBERTSON, and W. R. N. WILLIAMSON.

Vitexin, isolated from puriri wood, is shown to be a lævorotatory compound, $C_{21}H_{20}O_{10}$. Since its trimethyl ether on oxidation gave 8-formyltri-*O*-methylapigenin, it consists of an apigenin nucleus with a $\cdot C_6H_7O(OH)_4$ residue attached at the 8-position. Parallel with this the hydrolytic fission of tri-*O*-methylvitexin gave di-*O*-methyl*apo*vitexin which is shown to be 2-hydroxy-4 : 6-dimethoxyacetophenone with a $\cdot C_6H_7O(OH)_4$ residue in the 3-position. Oxidation of vitexin with periodic acid or sodium metaperiodate gives dehydro*seco*vitexin from which warm methanolic sulphuric acid removes D-glyceraldehyde as the dimethyl acetal, leaving a mixture of two isomeric di-*O*-methyl derivatives. Tentative structures for vitexin and the above degradation products are advanced.

THE yellow pigment, vitexin, along with homovitexin, from New Zealand puriri wood (*Vitex littoralis*), was first examined by Perkin [1] who proposed the empirical formula $C_{15}H_{14}O_7$ or $C_{17}H_{16}O_8$, prepared a polyacetate, and showed that on hydrolytic decomposition with alkali the compound gave phloroglucinol, *p*-hydroxybenzoic acid, and *p*-hydroxyacetophenone. Further, Perkin noted that vitexin gave the same degradation products as apigenin and formed a tetranitro-derivative which he subsequently showed to be tetranitroapigenin [2] in agreement with his earlier suggestion that vitexin might consist of an apigenin nucleus with a side-chain attached. To accommodate his results Perkin [2] revised the empirical formula for vitexin to $C_{21}H_{20}O_{10}$ and suggested that the compound was a very stable glucoside of apigenin with an abnormal mode of attachment of the sugar residue. Subsequently, Barger [3] examined Perkin's vitexin which he claimed was a product of the acid hydrolysis of saponarin, being formed along with saponaretin considered to be impure homovitexin. On the basis of molecular-weight determinations and acetyl values Barger concluded that vitexin had the empirical formula $C_{15}H_{14}O_7$ and was represented by structure (I) or (II); in a personal communication to Barger [3] Perkin suggested a third possibility (III), a conclusion supported later by Péteri.[4] On the other hand Nakaoki [5] claimed that the glycoside saponarin gives Barger's saponaretin on hydrolysis and this is then transformed by longer treatment with hot dilute acids into vitexin which is an optical isomeride of saponaretin. Further, Nakaoki concluded that vitexin had formula $C_{21}H_{22}O_{10}$ and contained alcoholic and phenolic hydroxyl groups, forming an octa-acetyl derivative. On fusion with alkali the hydriodic

[1] Perkin, *J.*, 1898, **73**, 1019.
[2] Perkin, *J.*, 1900, **77**, 422.
[3] Barger, *J.*, 1906, **89**, 121.
[4] Péteri, *J.*, 1939, 1635.
[5] Nakaoki, *J. Pharm. Soc. Japan*, 1944, **64**, No. 11*A*, 51; *Chem. Abs.*, 1952, **46**, 108.

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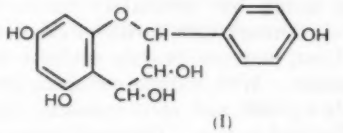
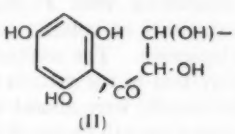
acid reduction product of vitexin gave *n*-hexanoic acid whilst on oxidation with permanganate vitexin furnished a substance which appeared to be 2 : 4 : 6-trihydroxyphenylacetic acid. Consequently Nakoaki concluded that vitexin was an apigenin derivative having a 2 : 3 : 4 : 5 : 6-pentahydroxy-*n*-hexyl residue attached at the 6- or 8-position, *e.g.*, formula (V; R = H, R′ = $C_6H_{13}O_5$). In connexion with the problem of the vitexin precursor it is of interest that Geissman and Kranen-Fielder [6] isolated glycosides of vitexin which do not give saponaretin as an intermediate product of hydrolysis.

On isolation from puriri wood by means of acetone without the intervention of mineral acids vitexin, m. p. 264—265°, has been found to be lævorotatory and is not appreciably racemised by prolonged boiling with 5% hydrochloric acid. From the analytical results obtained for the compound and for the numerous derivatives and degradation products now described it is clear that vitexin has the empirical formula $C_{21}H_{20}H_{10}$, as originally proposed by Perkin.[2] The compound does not contain a *C*-methyl group and on acetylation with boiling acetic anhydride and sodium acetate forms a hepta-acetate having a negative ferric reaction, whilst by the pyridine method a penta-acetate is formed, exhibiting a positive ferric reaction. Treatment of the penta-acetate with an excess of diazomethane furnished tetra-*O*-acetyldi-*O*-methylvitexin with a positive ferric reaction and giving di-*O*-methylvitexin on deacetylation. With methyl iodide and potassium carbonate in boiling acetone the penta-acetate gave rise to tetra-*O*-acetyltri-*O*-methylvitexin which on deacetylation yielded tri-*O*-methylvitexin with a negative ferric reaction; with ethyl iodide the corresponding tetra-*O*-acetyltri-*O*-ethylvitexin was obtained. By the Purdie method the trimethyl ether gave rise to a mixture of penta- and hexa-*O*-methylvitexin. The infrared absorption spectra of hepta-*O*-acetyl- and tetra-*O*-acetyltri-*O*-methyl-vitexin indicate the absence of a free hydroxyl group whereas the spectrum of the hexamethyl ether shows hydroxyl absorption.



(I)



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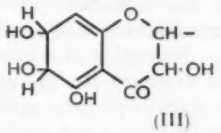

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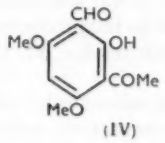
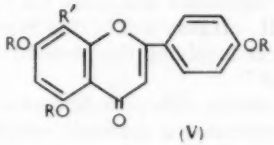
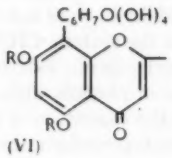


(IV)



(V)



(VI)

Hydrolytic decomposition of tri-*O*-methylvitexin with hot aqueous sodium hydroxide gave *p*-methoxyacetophenone and *p*-anisic acid but with boiling aqueous barium hydroxide an additional product, di-*O*-methyl*apo*vitexin $C_{14}H_{16}O_7(OMe)_2$, was obtained; the analogous di-*O*-ethyl*apo*vitexin has also been prepared. Both compounds gave ferric reactions and formed acyl derivatives. With an excess of aqueous periodic acid di-*O*-methyl*apo*vitexin gave rise to 3-formyl-4 : 6-di-*O*-methylphloracetophenone (IV) which was identified by reduction to 3-methyl-4 : 6-di-*O*-methylphloracetophenone and by comparison with a synthetic specimen. In this and similar periodate oxidations of vitexin and its derivatives the production of formaldehyde and a volatile acid fraction was observed but the amounts formed appeared to be too small to be significant. The formation of the 3-formylphloracetophenone residue clearly arises by the removal of a hydroxylated C_5-residue. Similarly, the oxidation of tri-*O*-methylvitexin with lead tetra-acetate

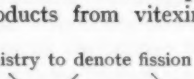
[6] Geissman and Kranen-Fielder, *Naturwiss.*, 1956, **43**, 226.

XUM

or by warm dilute nitric acid removed the same residue, giving 8-formyltri-*O*-methylapigenin (V; R = Me, R′ = CHO) which formed an oxime and a 2 : 4-dinitrophenylhydrazone and on reduction with a Raney nickel catalyst furnished 5 : 7 : 4′-trimethoxy-8-methylflavone (V; R = R′ = Me), identical with a synthetic specimen. From these degradations of di-*O*-methyl*apo*- and tri-*O*-methyl-vitexin, it is clear that tri-*O*-methylvitexin and consequently vitexin contain a C_6-system at the 8-position of the apigenin residue and may be represented by (V; R = Me) and (V; R = H) respectively. Further, of the ten oxygen atoms five are in the apigenin residue and are not concerned in the attachment of the C_6-system, because, from its conversion into 8-formyltri-*O*-methylapigenin, tri-*O*-methylvitexin contains a tri-*O*-methylapigenin residue. The remaining five oxygen atoms are contained in the C_6-moiety and, since hepta-*O*-acetyl- and tetra-*O*-acetyltri-*O*-methyl-vitexin do not contain a free hydroxyl group, this unit contains four active hydroxyl groups and an inert oxygen atom and consequently may be written $\cdot C_6H_7O(OH)_4$. This indifferent oxygen atom is not in a carbonyl group since vitexin does not show carbonyl activity and the infrared absorption spectra of tri- and hexa-*O*-methylvitexin indicated that the only carbonyl group present was conjugated in the nucleus, *i.e.*, the carbonyl of the apigenin residue. Therefore in the absence of a lactone or ester group it seemed likely that the fifth oxygen of the C_6-residue is in all probability present in an ether system and hence tri-*O*-methylvitexin and vitexin may be represented by the partial structure (VI; R = Me) and (VI; R = H) respectively.

To define the orientation of the hydroxyl system present in the C_6-residue a study of the oxidation of vitexin with varying quantities of periodic acid and sodium metaperiodate was undertaken. With aqueous periodic acid the oxidation of vitexin and its derivatives appeared to be abnormal; an excess of the reagent produced a comparatively rapid, initial reaction until about 1·5—2 mol. of periodic acid were used, followed by a gradually slowing oxidation but the results were somewhat variable. In all cases the initial stages of the oxidation were consistent with 1 : 2-glycol fission but ultimately traces of formaldehyde and small amounts of volatile acid were formed with further oxidation, *e.g.*, formation of 8-formylapigenin. The reaction did not, however, provide evidence for the presence of a glycerol system in the vitexin side-chain. With sodium metaperiodate in place of periodic acid the results were almost equally variable and again indicated that the reaction is not confined to a smooth fission of a 1 : 2-glycol system. The small amounts of formaldehyde were not regarded as significant and hence the C_6-residue did not appear to contain the system $\cdot CH(OH)\cdot CH_2\cdot OH$. It may well be that in addition to the production of 8-formylapigenin side reactions occur involving the phenolic apigenin residue (cf. the behaviour of phenols with periodic acid [7]).

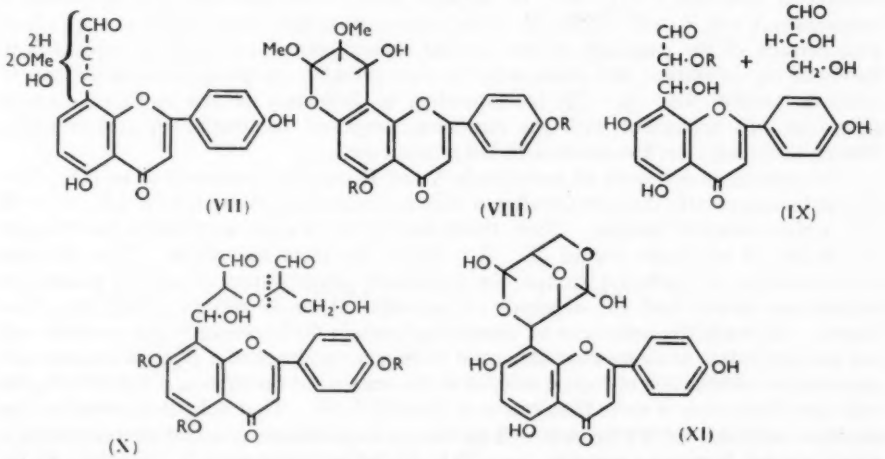
From the oxidation of methanolic vitexin with periodic acid or, more successfully, with sodium metaperiodate there readily separated a sparingly soluble, lævorotatory, yellow solid accompanied by small amounts of 8-formylapigenin. The composition of this product $C_{21}H_{18}O_{10}$ accords with oxidative fission of a cyclic 1 : 2-glycol system and accordingly it has been named dehydro*seco*vitexin.* Under similar conditions the oxidation of tri-*O*-methyl- and di-*O*-methyl*apo*-vitexin was somewhat erratic and the glycol scission products, dehydrotri-*O*-methyl*seco*- and dehydrodi-*O*-methyl*secoapo*-vitexin, which were somewhat difficult to purify, were accompanied by 8-formyltri-*O*-methylapigenin and 3-formyl-2-hydroxy-4 : 6-dimethoxyacetophenone respectively. The more satisfactory yields of dehydro*seco*vitexin may be due to the deposition of this product from the reaction mixture whereas the products from vitexin trimethyl ether and

* The prefix *seco* was introduced in steroid chemistry to denote fission of a ring with addition of a hydrogen atom at each carbon atom affected, *viz.*,  . Hydrogen is not added in the conversion of vitexin into the new compound, whence the prefix dehydro*seco* seems more appropriate.

[7] Pennington, *J. Amer. Chem. Soc.*, 1947, **69**, 187.

apo-vitexin dimethyl ether remain dissolved and are isolated with solvents; somewhat improved yields were obtained when one molecular proportion of oxidising agent was employed. Although dehydro*seco*vitexin reduced Fehling's solution and ammoniacal silver nitrate, it failed to form carbonyl derivatives and gave an infrared spectrum devoid of absorption in the aldehyde region, a result not entirely unexpected in the case of hydroxylated scission products from 1 : 2-cyclic glycols (cf. oxidation of 2 : 5-anhydro-D-mannitol [8]). Dehydro*seco*vitexin forms a penta-acetate with a negative ferric reaction and a penta-*p*-nitrobenzoate whilst dehydrotri-*O*-methyl*seco*vitexin gives a di-*p*-nitrobenzoate. Unlike vitexin or its ethers, dehydro*seco*-, dehydrotri-*O*-methyl*seco*-, and dehydrodi-*O*-methyl*secoapo*-vitexin are sensitive to acids. With a warm solution of 2 : 4-dinitrophenylhydrazine in dilute sulphuric acid these compounds gave a precipitate of the bis-2 : 4-dinitrophenylhydrazone of pyruvaldehyde which was also formed, more slowly, from penta-*O*-acetyldehydro*seco*vitexin under the same conditions. Distillation of these degradation compounds with dilute acids gave a distillate containing pyruvaldehyde but in alkaline media volatile carbonyl compounds were not formed. Further, with hot methanolic sulphuric acid dehydro*seco*vitexin gave in addition to pyruvaldehyde a mixture of two optically active crystalline products $C_{18}H_{12}O_6(OMe)_2$, A and B, which are readily separated by fractional crystallisation.

With regard to the source of the pyruvaldehyde derived from dehydro*seco*vitexin, it became clear, since vitexin is devoid of a *C*-methyl group, that this product was an artefact, the most probable source of which appeared to be the action of the mineral acid on glyceraldehyde or dihydroxyacetone, *i.e.*, $HO{\cdot}CH_2{\cdot}CH(OH){\cdot}CHO$ or $HO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OH \longrightarrow CH_3{\cdot}CO{\cdot}CHO + H_2O$. From a mixture obtained by heating dehydro*seco*vitexin with methanolic sulphuric acid a small amount of a neutral colourless oil was isolated which on treatment with warm acidic 2 : 4-dinitrophenylhydrazine yielded the bis-2 : 4-dinitrophenylhydrazone of pyruvaldehyde. With *p*-nitrobenzoyl chloride and pyridine this oil gave a di-*p*-nitrobenzoate found to be identical with the di-*p*-nitrobenzoate of D-glyceraldehyde dimethyl acetal; the corresponding diethyl acetal derivative of the



precursor was also prepared. Accordingly, therefore, it is clear that the scission of *seco*-vitexin with acids gives, in addition to the compounds A and B, D-glyceraldehyde, the formyl group of which is clearly produced by the scission of a 1 : 2-glycol system of vitexin with sodium metaperiodate or periodic acid.

With methyl iodide–potassium carbonate the compounds A and B form dimethyl

[8] Bera, Foster, and Stacey, *J.*, 1956, 4531.

ethers, $C_{15}H_{10}O_4(OMe)_4$, insoluble in aqueous sodium hydroxide and having negative ferric reactions. The infrared absorption spectra of each ether exhibits a hydroxyl band. In agreement with these compounds A and B form tri-*p*-nitrobenzoates, and the dimethyl ether of compound A or B gives a mono-*p*-nitrobenzote, thus confirming the presence of three hydroxyl groups in these degradation products.

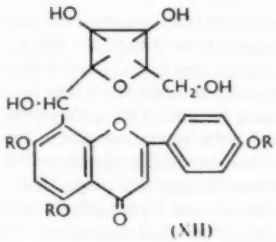
From the composition of compounds A and B, each of which contains two methoxyl groups, and from the ultraviolet absorption spectra of their dimethyl ethers it seemed reasonably certain that compounds A and B contained an apigenin residue retaining the three-carbon residue left after the removal of the glyceraldehyde moiety from dehydro-*seco*vitexin. Further, in vew of the formation of dehydro*seco*vitexin by periodic acid oxidation, this residual C_3 unit attached to the apigenin residue at the 8-position would be expected to contain an aldehyde or potential aldehyde group and, *inter alia*, could be written as a second glyceraldehyde residue as in formula (VII). From the properties of compounds A and B, including ferric reaction, solubilities in alkali, and methylation by a procedure which effects the alkylation of phenolic hydroxyl groups only (cf. methylation of phloridzin [9]), it seems clear that the hydroxyl groups at the 5- and the 4′-positions of the compounds are free and that the C_3 residue attached at the 8-position contains two methoxyl groups acquired during the treatment of dehydro*seco*vitexin with methanolic sulphuric acid; experiments have established that vitexin and 7-hydroxyflavone are not methylated by hot methanolic sulphuric acid. Further, the 7-hydroxyl group of the apigenin unit must be concerned in the attachment of this C_3 residue otherwise it would undergo methylation by potassium carbonate–methyl iodide simultaneously with the hydroxyl groups at the 5- and the 4′-position. Moreover, since the dimethyl ethers of compounds A and B contain a free alcoholic (and not phenolic) hydroxyl group and form *p*-nitrobenzoates the C_3 residue contains an alcoholic hydroxyl group. Thus compounds A and B are formed from dehydro*seco*vitexin by the loss of a glyceraldehyde residue with the simultaneous cyclisation and methylation of the residual hydroxylated side chain (containing a second glyceraldehyde residue). Of the possible expressions derived from (VII) the hemiacetal structure (VIII; R = H) appears best to accommodate the properties of compounds A and B, with (VIII; R = Me) representing their respective dimethyl ethers. This permits of the existence of two optical isomerides, which could be separated by fractional crystallisation and would arise by the cyclisation of an optically active glyceraldehyde residue (IX; R = H) corresponding to formation of the methyl α- and β-glycosides. In agreement with the structures proposed, compounds A and B reduce Fehling's solution after treatment with hot mineral acids.

The immediate precursor of compounds A and B may be considered to be (IX; R = Me) and consequently dehydro*seco*vitexin may be derived by the union of (IX; R = H) with a glyceraldehyde residue. From this a number of formulæ are possible for dehydro-*seco*vitexin, of which we regard (X; R = H) as the most acceptable. This structure accommodates the hydroxyl groups, the indifferent oxygen atom of vitexin retained in dehydro*seco*vitexin, and the aldehyde or potential aldehyde groups arising by glycol fission. Although the behaviour of vitexin and certain derivatives towards periodic acid and metaperiodate are somewhat abnormal there is no evidence of a glycerol scission with quantitative elimination of formic acid, or of the scission of the system ·CH(OH)·CH_2·OH with the elimination of more than traces of formaldehyde. That dehydro*seco*vitexin does not show carbonyl reactivity may well be due to its existence as a hemiacetal system of which several forms are possible, *e.g.*, (XI) (cf. sugar derivatives [8]). Further, in the scission of the oxide system in dehydro*seco*vitexin with methanolic sulphuric acid leading to the formation of compounds A and B the reaction would take place as indicated by the broken line in (X) with methylation of the precursor of compound A, to give (IX; R = Me) which would then cyclise and furnish the " glycoside " (VIII; R = H). Clearly this degradation of dehydro*seco*vitexin is facilitated by the activating carbonyl groups; the

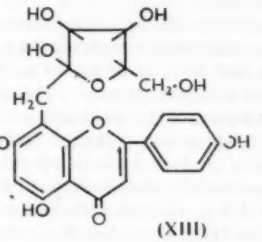
[9] Müller and Robertson, *J.*, 1933, 1170.

ready methanolysis invoked is comparable in some respects with the *O*-alkylation of α-hydroxy-ketones.[10] Consequently, vitexin and its trimethyl ether may be represented by formula (XII; R = H) and (XII; R = Me) respectively. This structure accounts for the optical activity, and preparation of phenolic trialkyl ethers and a hepta-acetate.

Whilst at present we regard the expression (XII; R = H) for vitexin as the best summation of our experimental results a number of alternative structures have been considered in detail, of which only (XIII) with dehydro*seco*vitexin as (XIV) need be mentioned now. Although formula (XIII) is in keeping with (*a*) the slight reduction of Fehling's solution by vitexin, (*b*) Nakaoki's claim to have isolated 2 : 4 : 6-trihydroxyphenylacetic acid, and (*c*) to some extent the behaviour of vitexin and tri-*O*-methylvitexin towards an excess of periodic acid and sodium metaperiodate, it appears to be excluded for the following reasons. Vitexin does not show carbonyl activity or form an osazone expected from (XIII) and is not methylated with methanolic sulphuric acid (cf. formation of fructosides); it only slowly reduces hot Fehling's solution and this is not unexpected in view of the behaviour of piscidic acid.[11] The residue (XV) left after the removal of



(XII)



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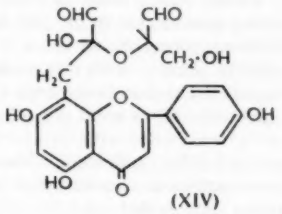

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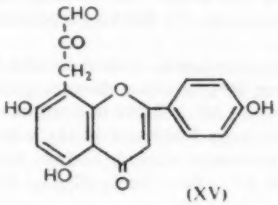

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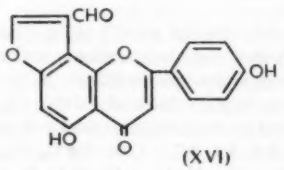

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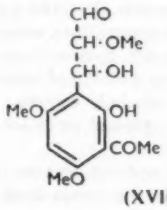

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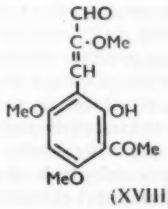
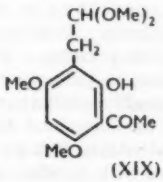


(XVIII)



(XIX)

glyceraldehyde from a dehydro*seco*vitexin having formula (XIV) would be optically inactive and with hot methanolic sulphuric acid would be expected to cyclise to an inactive benzofuran derivative (XVI).

The behaviour of di-*O*-methyl*apo*vitexin with periodic acid or sodium metaperiodate follows that of vitexin, resulting in the formation of dehydrodi-*O*-methyl*secoapo*vitexin; the rate of oxidation varies somewhat and the initial reaction was followed by a slower

[10] Bergmann and Gierth, *Annalen*, 1926, **448**, 48.
[11] Bridge, Coleman, and Robertson, *J.*, 1948, 257.

reaction with the absorption of varying amounts of reagent. With hot methanolic sulphuric acid this compound gives rise to pyruvaldehyde, probably by way of D-glyceraldehyde, and an optically inactive compound $C_{10}H_8O_2(OMe)_4$ which gives a ferric reaction and, from its composition and infrared absorption spectrum, appears to be the dimethyl acetal (XIX) of 3-acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde. If this view proves correct it seems likely that, after the removal of the D-glyceraldehyde moiety from dehydrodi-*O*-methyl*secoapo*vitexin, the residual system (XVII) undergoes rearrangement in the acid media with an intermediate (XVIII) from which extrusion of the formyl group occurs leaving a residue. This in acidic media re-arranges to give a phenylacetaldehyde (XIX) (cf. Zincke [12]). The ferric reaction given by this compound precludes a dicyclic system involving the hydroxy-group in the *ortho*-position to the acetyl residue of dehydrodi-*O*-methyl*secoapo*vitexin; the hydrogen bonding occurring in (XVII) would tend to inhibit the cyclisation to a substance corresponding to compound A.

Experimental

Vitexin.—This compound was isolated by Perkin's method,[1] and several modifications of it, but the following procedure gave superior yields and was adopted in large-scale work; the various methods gave identical products.

Finely milled wood of *Vitex littoralis* (20 kg.) was extracted in a continuous extractor with boiling acetone for 20 hr. and the concentrated extract (15 l.) decanted from a tar (A) (220 g.). On being concentrated to *ca.* 5 l. and kept at 0° for 24 hr. the extract deposited a crystalline solid (B) (52 g.) which was washed with hot acetone. The filtrate and washings from this were evaporated and on being kept a solution of the residual gum in boiling methanol (3 l.) deposited a greenish-yellow solid (C) (45 g.) which was collected and washed with warm acetone. The tar (A) was boiled with two portions of alcohol (each, 600 ml.), and the residual greenish-yellow solid (D) (25 g.) collected. The methanolic and alcoholic filtrates from (D) and (C), respectively, were combined, concentrated to 1·5 l., diluted with hot water (15 l.) and hydrochloric acid (1·5 l.), and boiled for 1 hr. After being decanted from a black tar which had separated and was discarded, the clear, orange solution was boiled for 5 hr. On cooling, this slowly deposited crude vitexin (E) (125 g.) in 24 hr.; a further quantity (F) (63·5 g.) separated in about 3 weeks.

The solids (B) (52 g.), (C) (45 g.), and (D) (25 g.) were combined, washed several times with boiling alcohol and then acetone, and recrystallised from 80% aqueous dioxan, giving vitexin in glistening yellow plates (83 g.), m. p. 264—265°, $[\alpha]_D^{20}$ −14·50° (*c* 2·789 in pyridine), $\lambda_{max.}$ 270 and 332 mμ (log ε 4·225 and 4·240), $\lambda_{min.}$ 248 and 282 mμ (log ε 3·949 and 4·011), which had not been in contact with mineral acid and gave a red ferric reaction in alcohol (Found: C, 58·4, 58·4, 58·6; H, 4·6, 4·8, 4·7. Calc. for $C_{21}H_{20}O_{10}$: C, 58·3; H, 4·7. Calc. for $C_{15}H_{14}O_7$: C, 58·8; H, 4·6. Calc. for $C_{21}H_{22}O_{10}$: C, 58·1; H, 5·1%).

Washed and recrystallised in the same manner, the combined solids (E) (125 g.) and (F) (63·5 g.) gave vitexin (132 g.), m. p. 264—265°, $[\alpha]_D^{20}$ −14·35° (*c* 2·414 in pyridine), identical with the foregoing specimen. Prolonged heating of either sample in 4 or 5% hydrochloric acid did not affect the specific rotation. The total yield of vitexin was 215 g. or 1·075% of wood.

Microcrystalline or pulverised vitexin is soluble in methanol, alcohol, acetone, or ethyl acetate and was readily soluble in pyridine and in hot dioxan, glycerol, phenol, or *cyclo*hexanone; larger crystals of the compound dissolve remarkably slowly.

Acetylation of vitexin (0·2 g.) with acetic anhydride (2 ml.) and sodium acetate (0·5 g.) at 100° for 1·5 hr. or with pyridine (5 ml.) and acetyl chloride (2 g.) on the steam-bath for 3 hr. gave the hepta-acetate which separated from acetone–methanol in colourless prisms or from acetic acid–alcohol in rhombs, m. p. 257—258°, $[\alpha]_D^{20}$ −73·2° (*c* 2·074 in acetone), with a negative ferric reaction in alcohol [Found: C, 57·9; H, 4·9; OAc, 41·3, 42·7. Calc. for $C_{21}H_{13}O_3(OAc)_7$: C, 57·9; H, 4·7; OAc, 41·5%].

A solution of vitexin (10 g.) in pyridine (100 ml.) and acetic anhydride (100 ml.) was heated on the steam-bath for 2 hr. and then slowly diluted with hot 2N-aqueous acetic acid (*ca.* 750 ml.) until crystals began to separate. On cooling, the mixture deposited the *penta-acetate* which crystallised from aqueous pyridine or methanol in faintly yellow needles; this derivative gave a deep red ferric reaction and melted at 146—147°, resolidified, and then melted again at 247°

[12] Zincke, *Annalen*, 1882, **216**, 298.

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(decomp.), $[\alpha]_D^{20}$ −4·43° (*c* 2·559 in acetone) [Found, in a specimen dried in a vacuum at 100° (mean of 5 analyses): C, 58·0; H, 4·8; Ac, 33·5. $C_{21}H_{15}O_5(OAc)_5$ requires C, 57·9; H, 4·7; Ac, 33·5%].

Tetra-O-*acetyldi*-O-*methylvitexin*.—On the addition of an excess of ethereal diazomethane to a solution of vitexin penta-acetate, m. p. 247° (1 g.), in methanol (5 ml.) a vigorous reaction ensued, the solution became red, and a yellow compound separated. The resulting *tetra*-O-*acetyldi*-O-*methylvitexin* separated from aqueous methanol and then absolute methanol in yellow needles, m. p. 205—206°, $[\alpha]_D^{20}$ −13·52° (*c* 1·08 in acetone), which gave a red ferric reaction [Found: C, 59·3; H, 5·2; OMe, 9·5. $C_{29}H_{26}O_{12}(OMe)_2$ requires C, 59·2; H, 5·1; OMe, 9·9%].

Ammonia (5 ml.; *d* 0·88) was added to this acetate (1 g.) in methanol (60 ml.) and 18 hr. later the solution was concentrated and gave *di*-O-*methylvitexin*, forming yellow needles from methanol with a deep red ferric reaction; on being heated it melted at 182°, solidified, and then melted at 264° [Found, in a specimen dried in a high vacuum: C, 59·8; H, 5·5; OMe, 12·5. $C_{21}H_{18}O_8(OMe)_2$ requires C, 60·0; H, 5·3; OMe, 13·5%]. With acetic anhydride–pyridine on the steam-bath for 2 hr. this compound, which is soluble in cold 2N-aqueous sodium hydroxide, regenerates the tetra-acetate, m. p. and mixed m. p. 205°.

Tetra-O-*acetyltri*-O-*methylvitexin*.—Methylation of the penta-acetate (4·15 g.), m. p. 247°, with potassium carbonate (40 g.) and methyl iodide (40 ml.) in boiling acetone (100 ml.) for 8 hr. gave a gum. A solution of this in warm pyridine was treated with hot water until solid began to separate and, on cooling, the mixture deposited a product which gave a faint red ferric reaction. Repetition of the methylation process with this material gave *tetra*-O-*acetyltri*-O-*methylvitexin*, forming from methanol colourless prisms (12·1 g.), m. p. 202°, $[\alpha]_D^{20}$ −9·82° (*c* 2·139 in acetone), which had a negative ferric reaction and on being heated melted at 202°, solidified, and then melted at 212°; a stable form, m. p. 212°, was occasionally obtained [Found: C, 59·5; H, 5·3; OMe, 13·9; OAc, 25·8. $C_{21}H_{13}O_3(OMe)_3(OAc)_4$ requires C, 59·8; H, 5·3; OMe, 14·5; OAc, 26·8%].

In boiling acetone (50 ml.) the interaction between vitexin penta-acetate (3 g.) and an excess of methyl iodide and potassium carbonate for 4 hr. gave a gum which on crystallisation from aqueous pyridine gave tetra-*O*-acetyldi-*O*-methylvitexin (1·3 g.), m. p. 198—199°, which, twice recrystallised from methanol, formed yellow needles, m. p. and mixed m. p. 204—205°, $[\alpha]_D^{20}$ −13·3° (*c* 1·626 in acetone), having a red ferric reaction. Addition of water to the aqueous-pyridine liquor precipitated a little tetra-*O*-acetyltri-*O*-methylvitexin which separated from aqueous pyridine and then methanol in prisms, m. p. and mixed m. p. 200—201°.

Deacetylation of tetra-*O*-acetyltri-*O*-methylvitexin (12·5 g.) in hot methanol (500 ml.) with ammonia (40 ml.; *d* 0·88) gave tri-*O*-methylvitexin as a *dihydrate* which was isolated from the concentrated reaction mixture, washed with acetone, and crystallised from methanol, forming colourless needles (8·5 g.), m. p. 288°, with a negative ferric reaction, insoluble in cold aqueous sodium hydroxide [Found: C, 56·4; H, 6·0; OMe, 17·8; OAc, negative. $C_{21}H_{17}O_7(OMe)_3,2H_2O$ requires C, 56·5; H, 5·9; OMe, 18·2%]. Acetylation of this ether by acetic anhydride–pyridine regenerated tetra-*O*-acetyltri-*O*-methylvitexin, m. p. and mixed m. p. 202° and 212°.

A mixture of tri-*O*-methylvitexin (0·1 g.), *p*-nitrobenzoyl chloride (0·3 g.), and pyridine (0·4 ml.) was heated on the steam-bath for ½ hr. and poured into dilute hydrochloric acid. The solid was triturated with aqueous sodium hydrogen carbonate, washed, and crystallised from methanol and then acetone–methanol, giving the *tetra*-p-*nitrobenzoate* of tri-*O*-methylvitexin in colourless feathery needles, m. p. 176°, with a negative ferric reaction [Found: N, 5·2, 5·3; OMe, 9·1. $C_{49}H_{29}O_{19}N_4(OMe)_3$ requires N, 5·4; OMe, 8·9%].

Tri-O-*ethylvitexin*.—Vitexin acetate (6·5 g.), m. p. 247°, was heated with ethyl iodide (20 ml.) and potassium carbonate (10 g.) in boiling acetone (150 ml.) for 16 hr. and the gummy product isolated and crystallised from aqueous pyridine and then methanol. This solid was again heated with ethyl iodide (10 ml.) and potassium carbonate (5 g.) in acetone (50 ml.) for 5 hr. Crystallised from aqueous pyridine and then methanol, the resulting *tetra*-O-*acetyltri*-O-*ethylvitexin* formed colourless prisms (3·9 g.), m. p. 236°, with a negative ferric reaction (Found: C, 61·4; H, 5·4. $C_{35}H_{40}O_{14}$ requires C, 61·4; H, 5·9%). Deacetylation of this compound (3·5 g.) with ammonia (15 ml.; *d* 0·88) in methanol (100 ml.) at room temperature for 24 hr. gave *tri*-O-*ethylvitexin* which separated from methanol in colourless needles (2·6 g.), m. p. 270°, having a negative ferric reaction (Found, in a specimen dried in a high vacuum: C, 63·0; H, 6·0. $C_{27}H_{32}O_{10}$ requires C, 62·8; H, 6·2%).

In one experiment the tetra-*O*-acetyltri-*O*-ethylvitexin was accompanied by a small amount

of a compound which appeared to be a *tetra*-O-*acetyldi*-O-*ethylvitexin* which separated first on the gradual addition of water to a solution of the reaction product in hot pyridine. Recrystallised several times from aqueous pyridine and then methanol, the diethyl derivative formed clusters of yellow needles, m. p. 187·5°, with an intense red-brown ferric reaction (Found: C, 59·8; H, 5·6. $C_{33}H_{36}O_{14}$ requires C, 60·3; H, 5·5%).

Penta- and Hexa-O-*methylvitexin*.—A mixture of tri-*O*-methylvitexin (11 g.), silver oxide (25 g.), methyl iodide (40 g.), and acetone (500 ml.) was heated under reflux for 50 hr. The gum left on evaporation of the filtered mixture was heated in boiling methyl iodide (40 ml.), containing silver oxide (15 g.), with the addition of more iodide (40 ml.), for 24 hr. On isolation, the gummy product was dissolved in boiling benzene (100 ml.), and the hot solution slowly treated with light petroleum (b. p. 40—60°) until it became faintly opalescent. After having been kept at room temperature for 2 hr., the liquor was decanted from a little oil which had separated, heated to the b. p., and treated with more light petroleum (40 ml.). A little more oil then separated and this process was repeated, a crystalline solid ultimately separating. This was removed and the mother-liquor poured into an excess of boiling light petroleum (b. p. 40—60°), giving when cold more crystalline solid. The combined solid fractions were washed with benzene, leaving crude *hexa*-O-*methylvitexin* (1·6 g.), m. p. 190—200°, which on purification from benzene–light petroleum (b. p. 60—80°) and then benzene, formed glistening colourless needles, m. p. 205°, $[\alpha]_D^{20}$ +13·45° (*c* 1·784 in MeOH), with a negative ferric reaction [Found: C, 62·7; H, 6·6; OMe, 36·8. $C_{21}H_{14}O_4(OMe)_6$ requires C, 62·8; H, 6·2; OMe, 36·0%].

The benzene washings of the crude hexamethyl ether were added to the combined oils which had been precipitated first with light petroleum and on being kept the solution deposited more hexamethyl ether which was isolated. Concentration of the benzene liquor then gave *penta*-O-*methylvitexin* (1 g.), m. p. 220°, which was boiled with benzene to remove traces of the hexamethyl ether, and then crystallised from from ethyl acetate–acetone, forming colourless glistening prisms, m. p. 234°, with a negative ferric reaction [Found: C, 62·2; H, 6·2; OMe, 32·0. $C_{21}H_{15}O_5(OMe)_5$ requires C, 62·1; H, 6·0; OMe, 30·9%].

By fractionation of the residues from benzene and light petroleum more crude penta- (0·6 g.), m. p. 220°, and hexa-methyl ether (1·7 g.), m. p. 190°, were obtained.

A mixture of penta-*O*-methylvitexin (50 mg.), *p*-nitrobenzoyl chloride (0·15 g.), and pyridine (1 ml.) was heated on the steam-bath for 30 min., cooled, and poured into dilute hydrochloric acid. After having been triturated with aqueous sodium hydrogen carbonate and washed with water, the solid was crystallised from acetone–methanol, giving the p-*nitrobenzoate* of penta-*O*-methylvitexin in colourless glistening prisms, m. p. 277° [Found: C, 60·1; H, 5·3; N, 2·2, 2·3; OMe, 26·2. $C_{28}H_{18}O_8N(OMe)_5$ requires C, 60·8; H, 5·1; N, 2·2; OMe, 25·3%].

Hydrolytic Fission of Tri-O-*methylvitexin*.—(*a*) A mixture of tri-*O*-methylvitexin (2 g.) and 8% aqueous sodium hydroxide (100 ml.) in nitrogen was boiled until a homogeneous solution was formed. A current of steam was then led into the boiling solution, and the distillate (150 ml.) collected. A small portion of the distillate was treated with aqueous 2 : 4-dinitrophenylhydrazine sulphate, giving a copious precipitate of *p*-methoxyacetophenone 2 : 4-dinitrophenylhydrazone which, on purification by chromatography from benzene on aluminium oxide followed by crystallisation from ethylene glycol or ethyl acetate, had m. p. and mixed m. p. 256° (0·38 g.) (Found: N, 17·0. Calc. for $C_{15}H_{14}O_5N_4$: N, 17·0%). From the remainder of the distillate *p*-methoxyacetophenone was isolated with ether and converted into the semicarbazone (0·46 g.), m. p. and mixed m. p. 198° (Found: C, 57·8; H, 6·3; N, 20·0. Calc. for $C_{10}H_{13}O_2N_3$: C, 58·0; H, 6·3; N, 20·3%).

The brown solid obtained by acidification of the residual alkaline liquor was crystallised from methanol, giving *p*-anisic acid (0·23 g.), m. p. and mixed m. p. 182° (Found: C, 63·3; H, 5·4. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·3%), which formed the amide, m. p. and mixed m. p. 164° (Found: N, 9·4. Calc. for $C_8H_9O_2N$: N, 9·3%).

(*b*) A rapid stream of nitrogen was passed through boiling saturated aqueous barium hydroxide (200 ml.), containing tri-*O*-methylvitexin (2 g.), for 2 hr. and the effluent gas led into aqueous 2 : 4-dinitrophenylhydrazine, giving a precipitate of *p*-methoxyacetophenone 2 : 4-dinitrophenylhydrazone (0·08 g.), m. p. 256°. The hot homogeneous alkaline liquor was acidified with dilute sulphuric acid, cooled, and filtered and the solid extracted with boiling methanol, giving *p*-anisic acid (0·55 g.), m. p. 182°. The filtrate was treated with a little barium carbonate, filtered, and evaporated in a vacuum at 40°, leaving a pale yellow product which on crystallisation from dioxan gave *di*-O-*methyl*apo*vitexin* in rosettes of colourless needles (0·95 g.), m. p.

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ca. 137°. After repeated purification from alcohol–light petroleum (b. p. 60—80°) or from acetone, this compound melted at 126—130°, solidified, and then melted at 222° (decomp.), having $[\alpha]_D^{20}$ +4·59° (*c* 1·417 in MeOH) [Found: C, 53·2; H, 6·3; OMe, 16·8. $C_{14}H_{16}O_7(OMe)_2$ requires C, 53·6; H, 6·2; OMe, 17·3%]. This neutral product was soluble in chloroform, acetic acid, pyridine, or warm alcohol and gave a deep red ferric reaction in alcohol and an emerald-green colour with Gibbs's reagent.

A mixture of di-*O*-methyl*apo*vitexin (50 mg.), *p*-nitrobenzoyl chloride (0·2 g.), and pyridine (1 ml.) was heated on the steam-bath for ½ hr. On isolation the *penta*-p-*nitrobenzoate* formed almost colourless needles, m. p. 192°, from acetone–methanol, with a negative ferric reaction [Found: C, 54·9; H, 3·7; N, 6·2; OMe, 5·6. $C_{49}H_{31}O_{22}N_5(OMe)_2$ requires C, 55·5; H, 3·4; N, 6·4; OMe, 5·6%]. Acetylated with acetic anhydride and sodium acetate, di-*O*-methyl*apo*vitexin gave an acetate which separated from light petroleum in colourless needles, m. p. 151—152°, with a negative ferric reaction.

3-*Formyl*-2-*hydroxy*-4 : 6-*dimethoxyacetophenone*.—A solution of 6% aqueous para-periodic acid (10 ml.) was added to di-*O*-methyl*apo*vitexin (0·2 g.) in acetic acid (10 ml.), and the mixture agitated for 5 hr., diluted with water (100 ml.), neutralised with a slight excess of sodium hydrogen carbonate, and then kept for 16 hr. On isolation the yellow deposit was digested with hot methanol (10 ml.) and, on cooling, the extract deposited 3-formyl-2-hydroxy-4 : 6-dimethoxyacetophenone in pale yellow-green tablets (0·13 g.), m. p. and mixed m. p. 170° (Found: C, 58·6; H, 5·3. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). The 2 : 4-dinitrophenylhydrazone separated from acetic acid in orange-red needles, m. p. 259°, identical with a synthetical specimen.

The aqueous liquors left after the separation of the crude 3-formyl-2-hydroxy-4 : 6-dimethoxyacetophenone contained formaldehyde, isolated as the 2 : 4-dinitrophenylhydrazone (85 mg.), m. p. and mixed m. p. 158°.

Synthetic 3-formyl-2-hydroxy-4 : 6-di-*O*-methoxyacetophenone was prepared by the following modification of Gruber and Traub's method.[13] The solid formed by the interaction of 2-hydroxy-4 : 6-dimethoxyacetophenone (5 g.), hydrogen cyanide (10 ml.), and aluminium chloride (6 g.) in ether (150 ml.), saturated at 0° with hydrogen chloride, during 24 hr., was dissolved in water (250 ml.), and the solution almost neutralised with 2N-aqueous sodium hydroxide. On being kept at 80° for 45 min. this gave the formyl-ketone which separated from alcohol in greenish-yellow needles or from ethyl acetate in tablets (5·4 g.), m. p. 170°. The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in red needles, m. p. 259° (Found: N, 14·2. $C_{17}H_{16}O_8N_4$ requires N, 14·0%).

Reduction of 3-formyl-2-hydroxy-4 : 6-dimethoxyacetophenone (4 g.) with zinc amalgam (10 g.) in acetic acid (30 ml.) and concentrated hydrochloric acid (8 ml.) for 2—3 min. and dilution of the filtered mixture with water gave 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone [14] (2·5 g.), m. p. and mixed m. p. 144°, after purification from alcohol.

Hydrolytic Fission of Tri-O-*ethylvitexin*.—Tri-*O*-ethylvitexin (2 g.) was heated in boiling saturated aqueous barium hydroxide (100 ml.) for 3 hr. and the cooled mixture treated with carbon dioxide, filtered, and evaporated in a vacuum. From the residue boiling methanol extracted a gum which on crystallisation from dioxan, containing a little ether, gave *di*-O-*ethyl*-apo*vitexin* which on recrystallisation from acetone formed pale yellow needles, m. p. 203·5—204°, with a red ferric reaction in alcohol [Found: C, 56·1; H, 6·9; OEt, 22·9. $C_{14}H_{16}O_7(OEt)_2$ requires C, 55·9; H, 6·8; OEt, 23·3%]. The *penta*-p-*nitrobenzoate* separated from acetone–methanol in almost colourless needles, m. p. 175°, with a negative ferric reaction [Found: C, 55·7; H, 3·8; N, 6·2; OEt, 8·3. $C_{49}H_{31}O_{22}N_5(OEt)_2$ requires C, 56·2; H, 3·7; N, 6·2; OEt, 8·0%].

Oxidation of Tri-O-*methylvitexin with Lead Tetra-acetate*.—(*a*) A mixture of the ether (1·5 g.), lead tetra-acetate (4·5 g.), and acetic acid (25 ml.) was kept at 25° for 5 days, poured into water (100 ml.), and extracted with chloroform. The combined chloroform extracts from 5 experiments were washed with 2N-aqueous sodium hydrogen carbonate, dilute aqueous sodium hydroxide, and then water, dried, and evaporated, leaving a yellow product (2·5 g.) which was triturated thrice with acetone (3 ml.). Crystallised from alcohol, the residue gave 8-*formyl*-5 : 7 : 4′-*trimethoxyflavone* in pale yellow plates (0·45 g.), m. p. 237° (decomp.), with a negative ferric reaction [Found: C, 66·6; H, 5·1; OMe, 25·4. $C_{16}H_7O_3(OMe)_3$ requires C, 67·0; H, 4·7;

[13] Gruber and Traub, *Monatsh.*, 1947, **77**, 414.
[14] Curd and Robertson, *J.*, 1933, 437.

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OMe, 27·4%]. The 2 : 4-dinitrophenylhydrazone was an unstable red solid, m. p. 250—254° (decomp.). By the hydroxylamine–pyridine method the formylflavone gave a derivative which had the composition of a *dioxime*, forming almost colourless needles, m. p. 232° (decomp.), from methanol (Found: C, 61·8; H, 5·6; N, 7·2. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9; N, 7·6%). Treatment of the aqueous liquors left after precipitation of the 8-formyl-5 : 7 : 4′-trimethoxyflavone with 2 : 4-dinitrophenylhydrazine and with dimedone gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159°, and the dimedone derivative, m. p. and mixed m. p. 188°, of formaldehyde.

Reduction of 8-formyl-5 : 7 : 4′-trimethoxyflavone (0·4 g.) with hydrogen at 60 lb./sq. in. and Raney nickel W.5 catalyst [15] in dioxan (50 ml.) gave a product, which on repeated crystallisation from benzene–light petroleum (b. p. 60—80°) formed rosettes of colourless needles (0·15 g.), m. p. 228°, undepressed on admixture with a specimen of synthetic 5 : 7 : 4′-trimethoxy-8-methylflavone, m. p. 230°, prepared by the following method.

A mixture of 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone (13 g.), *p*-anisoyl chloride (12 g.), and pyridine (75 ml.) was heated on the steam-bath for 3 hr., cooled, and poured into water (500 ml.). Crystallised from 95% alcohol and washed, the resulting solid gave 2-p-*anisoyloxy*-4 : 6-*dimethoxy*-3-*methylacetophenone* in needles (16 g.), m. p. 169° (Found: C, 65·7; H, 5·9. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·9%. Heated with pulverised sodamide (35 g.) in boiling benzene (75 ml.) for 4 hr. this keto-ester (7 g.) gave 2-*hydroxy*-4 : 6 : 4′-*trimethoxy*-3-*methyldibenzoylmethane* which was separated from the crude reaction product with aqueous sodium hydroxide and recovered by acidification of the extracts with acetic acid and isolation with chloroform. Crystallised from alcohol and then acetone–light petroleum (b. p. 60—80°), the diketone formed yellow-green needles (4 g.), m. p. 184° (decomp.), with an emerald-green ferric reaction (Found: C, 66·6; H, 5·6. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·9%). The *monoxime* separated from alcohol in colourless needles, m. p. 188° (Found: N, 4·0. $C_{19}H_{21}O_6N$ requires N, 3·9%). Cyclised with 75% sulphuric acid (30 ml.) at room temperature in 10 min., this diketone (2·5 g.) gave 5 : 7 : 4′-*trimethoxy*-8-*methylflavone* which separated from benzene in needles (2·3 g.), m. p. 230° (decomp.) (Found: C, 70·4; H, 5·3. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%). The natural and the synthetic specimen had identical ultraviolet absorption spectra.

(*b*) Oxidation of tri-*O*-methylvitexin (1·5 g.) was effected with lead tetra-acetate (4·5 g.) in acetic acid (20 ml.) at 18° for 4 days and the mixture poured into water (150 ml.). The resinous, brownish-yellow precipitate from three experiments was washed with water and dissolved in methanol (20 ml.). On being kept for a week this solution deposited the trimethyl ether of dehydro*seco*vitexin (0·7 g.), m. p. 194° (decomp.), which on recrystallisation from methanol–pyridine formed tiny pale yellow needles, m. p. 201—202° (decomp.), identical with the product obtained by periodic acid oxidation.

Oxidation of Tri-O-methylvitexin with Nitric Acid.—A mixture of tri-*O*-methylvitexin (0·3 g.), concentrated nitric acid (5 ml.), and water (25 ml.) was heated under reflux for 1·5 hr., cooled, and filtered to remove a little *p*-anisic acid, m. p. and mixed m. p. 180°, which had separated. The filtrate was basified with a slight excess of 2N-aqueous sodium hydroxide and extracted with chloroform (15 ml. × 4). Evaporation of the dried extracts left 8-formyl-5 : 7 : 4′-trimethoxyflavone which separated from alcohol in needles, m. p. and mixed m. p. 236°.

Oxidation of Tri-O-methylvitexin with Periodic Acid.—(*a*) 0·5N-Periodic acid (35 ml.) was added to a solution of the ether (1 g.) in methanol (150 ml.), and the mixture kept in the dark for 10 hr., filtered, and neutralised (phenolphthalein) with aqueous barium hydroxide. On being evaporated to 50 ml. the filtered solution deposited an intractable resin which was removed, and the liquor was extracted with chloroform (50 ml. × 3). Evaporation of the combined dried extracts left a yellow solid (0·1 g.) which was triturated with acetone (5 ml.) and crystallised from alcohol, giving 8-formyl-5 : 7 : 4′-trimethoxyflavone in pale yellow needles (50 mg.), m. p. and mixed m. p. 235°; in another experiment under similar conditions 7·5 g. of trimethyl ether gave 0·45 g. of the formylflavone.

(*b*) 0·5N-Aqueous periodic acid (70 ml.) was added in portions of 10 ml. at intervals of 1 hr. to a stirred solution of tri-*O*-methylvitexin (2 g.) in acetic acid (40 ml.). The mixture was diluted with excess of saturated aqueous sodium hydrogen carbonate at 35° and kept at room temperature for 4 days. The resulting precipitate was washed with water, dried, and extracted with boiling methanol (15 ml.). On being kept the extract slowly deposited *dehydrotri*-O-*methylseco-vitexin* (0·9 g.), m. p. 197—198°, which on recrystallisation from pyridine–methanol or much

[15] Mozingo, *Org. Synth.*, 1941, **21**, 15.

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methanol had m. p. 201—202° [Found: C, 61·4, 61·0, 60·8; H, 5·4, 5·7, 5·7; OMe, 20·8. $C_{21}H_{15}O_7(OMe)_3$ requires C, 61·0; H, 5·1; OMe, 19·7%].

The use of sodium metaperiodate in place of periodic acid gave the same product, m. p. and mixed m. p. 200° (1·3 g. from 6 g. of tri-*O*-methylvitexin). With either reagent the yield was variable.

Oxidation of Tri-O-methylvitexin with Sodium Metaperiodate in Aqueous Methanol at Room Temperature.—

Experiment 1.

Time	25 min.	45 min.	113 min.	16 hr.
$NaIO_4$, mols.	1·77	2·64	3·97	5·38

Experiment 2.

Time	20 min.	32 min.	47 min.	61 min.	115 min.
$NaIO_4$, mols.	1·13	1·63	1·73	1·92	2·14

On being distilled, a solution of the dehydrotri-*O*-methyl*seco*vitexin (0·2 g.) in a mixture of methanol (10 ml.), water (10 ml.), and concentrated sulphuric acid (2 ml.) gave a distillate containing pyruvaldehyde which was isolated as the bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 299—300° (Found: C, 41·7; H, 3·1; N, 25·2. Calc. for $C_{15}H_{12}O_8N_8$: C, 41·7; H, 2·8; N, 25·9%), and as the bisphenylhydrazone which separated from dilute alcohol in pale yellow needles, m. p. 145° (Found: C, 71·3; H, 6·5; N, 22·0. Calc. for $C_{15}H_{16}N_4$: C, 71·4; H, 6·4; N, 22·2%).

The *di*-p-*nitrobenzoate* of the dehydrotri-*O*-methyl*seco*vitexin separated from acetone–methanol in almost colourless needles, m. p. 159—160° (Found: N, 3·7. $C_{35}H_{30}O_{16}N_2$ requires N, 3·6%). Acetylation of the trimethyl ether (0·2 g.) with pyridine (5 ml.) and acetic anhydride (1·5 ml.) gave a *product* which separated from benzene–light petroleum (b. p. 60—80°) in colourless needles, m. p. 94° [Found: C, 60·6; H, 4·4. $C_{28}H_{28}O_{12}$ (diacetate) requires C, 60·4; H, 5·1. $C_{28}H_{26}O_{11}$ (anhydro-diacetate) requires C, 62·4; H, 4·8%].

*Dehydroseco*vitexin.—A solution of vitexin (8·3 g.) was prepared by heating an excess of vitexin in boiling methanol (1 l.) containing water (300 ml.) for 2 hr. The filtered solution was quickly cooled and treated with sodium metaperiodate (15 g.) in water (1 l.), and the mixture diluted with water to 4·5 l. The solid which had separated from this during 20 hr. was isolated, washed with water and then acetone, and recrystallised from aqueous pyridine and then from much methanol–acetone, giving *dehydroseco*vitexin in pale yellow prisms (4·2 g.), m. p. >360°, $[\alpha]_D^{20}$ −147° (*c* 1·0 in pyridine) (Found, in a specimen dried at 105°: C, 58·5; H, 4·5. $C_{21}H_{18}O_{10}$ requires C, 58·6; H, 4·2%). This compound had a deep red ferric reaction in alcohol, rapidly reduced Fehling's solution and gave a silver mirror with ammoniacal silver nitrate at 50—60° in *ca.* 30 min. With acetic anhydride–pyridine it gave a *penta-acetate* which separated from 50% acetic acid and then acetone–methanol in colourless needles, m. p. 242°, $[\alpha]_D^{20}$ −68·25° (*c* 0·7325 in acetic acid), with a negative ferric reaction (Found: C, 58·0, 58·2; H, 4·4, 4·7. $C_{31}H_{28}O_{15}$ requires C, 58·1; H, 4·4%). The *penta*-p-*nitrobenzoate* crystallised from acetone–methanol in pale brownish needles, m. p. 225° (Found: N, 6·0. $C_{56}H_{33}O_{25}N_5$ requires N, 6·0%).

Dehydro*seco*vitexin was also obtained by adding a solution of sodium metaperiodate (10 g.) in water (300 ml.) to a slurry of vitexin (10 g.) in alcohol (300 ml.) and stirring the mixture for 24 hr.; the purified compound (6·35 g.) had $[\alpha]_D^{20}$ −146·5° (*c* 0·7165 in pyridine). In a series of experiments in daylight at room temperature it was found that after 17 hr., various amounts of sodium periodate were consumed, *e.g.*, 1·50, 1·69, 1·85, 2·07, 2·60, 3·11, 3·25 mols. In the absence of light at 0° the corresponding amounts varied from 1·08 to 1·19 mols.

The aqueous filtrate and washings from crude dehydro*seco*vitexin were concentrated in a vacuum and repeatedly extracted with ether. Evaporation of the combined washed and dried extracts gave 8-*formylapigenin* which separated from methanol in slender yellow needles (0·628 g.), m. p. 301°, and was optically inactive (Found, in material dried in a high vacuum: C, 64·0; H, 3·5. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%). This compound, which had a deep red ferric reaction, formed an acetate, m. p. 176°, and on methylation by methyl iodide–potassium carbonate in boiling acetone gave a small yield of 8-formyl-5 : 7 : 4′-trimethoxyflavone, m. p. and mixed m. p. 236°.

A solution of dehydro*seco*vitexin (0·1 g.) in methanol (10 ml.) and concentrated sulphuric

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acid (10 ml.) was distilled with the addition of water (10 ml.) during the distillation, and the distillate treated with aqueous 2 : 4-dinitrophenylhydrazine sulphate. Crystallised from dioxan, the precipitate gave the bis-2 : 4-dinitrophenylhydrazone of pyruvaldehyde, m. p. and mixed m. p. 299—300° (Found: N, 25·2. Calc. for $C_{15}H_{12}O_8N_8$: N, 25·9%). With phenylhydrazine the distillate gave the bisphenylhydrazone of pyruvaldehyde, forming pale yellow needles, m. p. and mixed m. p. 145° (Found: N, 22·0. Calc. for $C_{15}H_{16}N_4$: N, 22·2%).

The same results were obtained when the compound was heated with dioxan and concentrated hydrochloric acid.

Compounds A and B.—(*a*) A mixture of dehydro*seco*vitexin (10·1 g.), absolute methanol (350 ml.), and concentrated sulphuric acid (10 ml.) was heated under reflux for 2·5 hr., the cooled, clear yellow solution was diluted with ether (1500 ml.), and the ethereal solution separated and extracted several times with aqueous sodium hydrogen carbonate. Acidification of the washings followed by treatment with aqueous 2 : 4-dinitrophenylhydrazine sulphate gave the bis-2 : 4-dinitrophenylhydrazone of pyruvaldehyde. The semisolid material left on evaporation of the dried ether solution was dissolved in much acetone and the solution concentrated until solid began to separate and cooled. On isolation the product was recrystallised several times from acetone, giving *compound A* in pale yellow prisms (1·1 g.), m. p. above 360°, $[\alpha]_D^{20}$ +90·5° (*c* 1·1 in pyridine) [Found: C, 62·4, 62·1; H, 4·9, 5·0; OMe, 15·8, 15·9. $C_{18}H_{12}O_6(OMe)_2$ requires C, 62·2; H, 4·7; OMe, 16·1%]. The *tri*-p-*nitrobenzoate* of this compound separated from acetone in almost colourless needles, m. p. 277° (Found: N, 5·1. $C_{41}H_{27}O_{17}N_3$ requires N, 5·0%). Prepared by methyl iodide–potassium carbonate, the *dimethyl ether* formed colourless needles, m. p. 247—249°, $[\alpha]_D^{20}$ +86·3° (*c* 0·0183 in MeOH), from acetone and then methanol, having a negative ferric reaction [Found: C, 64·0; H, 5·6; OMe, 29·3. $C_{18}H_{10}O_4(OMe)_4$ requires C, 63·8; H, 5·4; OMe, 29·9%]. The p-*nitrobenzoate* of this dimethyl ether crystallised from methanol in pale yellow needles, m. p. 145° (Found: N, 2·5. $C_{29}H_{25}O_{11}N$ requires N, 2·5%).

The acetone filtrate from crude compound A was mixed with ethyl acetate and the greater part of the acetone distilled. On being kept the residue deposited *compound B* (3·5 g.) which crystallised from ethyl acetate in yellow prisms, decomposing at 188—190° after sintering at 178°, $[\alpha]_D^{20}$ −118° (*c* 3·5 in pyridine), with a red ferric reaction [Found, in a specimen dried at room temperature: C, 59·9; H, 5·1; OMe, 14·4, 14·4. $C_{18}H_{12}O_6(OMe)_2,H_2O$ requires C, 59·4; H, 5·0; OMe, 15·3. Found, in a specimen dried in a high vacuum at 135—150°: C, 62·1; H, 4·8. $C_{20}H_{16}O_8$ requires C, 62·2; H, 4·7%]. Tha *tri*-p-*nitrobenzoate* formed pale brown needles, m. p. 254—255° (decomp.), from acetone (Found: N, 5·1; OMe, 7·4. $C_{40}H_{24}O_{16}N_3$·OMe requires N, 5·0; OMe, 7·5%). The *deimthyl ether* of compound B separate from acet one and then methanol in colourless needles, m. p. 251—252°, $[\alpha]_D^{20}$ −68·5° (*c* 0·206 in MeOH), with a negative ferric reaction [Found: C, 63·7, 63·4; H, 5·8, 5·7; OMe, 29·1. $C_{18}H_{10}O_4(OMe)_4$ requires C, 63·8; H, 5·4; OMe, 29·9%]. The *p*-nitrobenzoate of this dimethyl ether crystallised from methanol in almost colourless needles, m. p. 124—126° (Found: N, 2·5. $C_{29}H_{25}O_{11}N$ requires N, 2·5%).

(*b*) A mixture of dehydro*seco*vitexin (2·0 g.), methanol (80 ml.), and concentrated sulphuric acid (2·0 ml.) was heated under reflux for 2 hr. and the cooled clear yellow solution poured into water containing an excess of barium carbonate. ½ Hour later the filtered mixture was treated with more barium carbonate, filtered, and evaporated in a vacuum with the addition of several portions of benzene (50 ml.) during the evaporation. The residue was twice extracted with warm acetone and the filtered extracts were evaporated, leaving a viscous oil, a sample of which gave the bis-2 : 4-dinitrophenylhydrazone of pyruvaldehyde with the acidic reagent. After being washed with ether this product was dissolved in a little pyridine and treated with excess of *p*-nitrobenzoyl chloride on the steam-bath for 1·5 hr. On isolation in the usual manner the crude solid was triturated with aqueous sodium hydrogen carbonate, washed, dried, and extracted with hot ligroin (b. p. 100—120°). Crystallised from the same solvent and then from methanol, and finally aqueous methanol, the extract gave the *bis*-p-*nitrobenzoate* of D-glyceraldehyde dimethyl acetal in clusters of needles, m. p. 104—106°, $[\alpha]_D^{18}$ +59·6° (*c* 0·054 in $CHCl_3$) Found, in a specimen dried in a high vacuum at 80°: C, 52·5; H, 4·3; N, 6·8; OMe, 13·3. $C_{17}H_{13}O_8N_2(OMe)_2$ requires C, 52·5; H, 4·2; N, 6·5; OMe, 14·3%] (yield, 0·3 g. from 2 g. of *seco*vitexin); admixture with an authentic specimen, m. p. 107—108°, did not depress the m. p. of this bis-*p*-nitrobenzoate; the infrared absorption spectra of the compounds from the two sources were identical. In another experiment with dehydro*seco*vitexin (2 g.) the aqueous

distillate was collected and poured into acidic 2 : 4-dinitrophenylhydrazine, giving a precipitate of pyruvaldehyde bis-2 : 4-dinitrophenylhydrazone (0·5 g.), m. p. 304°, after purification from acetic acid. The residue from the distillation gave the bis-*p*-nitrobenzoate of glyceric aldehyde dimethyl acetal, m. p. 104—106°.

A specimen of the synthetic bis-*p*-nitrobenzoate of D-glyceraldehyde dimethyl acetal[16] was prepared from D-glyceraldehyde dimethyl acetal by the pyridine method. The compound separated from aqueous methanol in clusters of colourless needles, m. p. 107—108°, $[\alpha]_D^{15}$ +71·73° (*c* 0·590 in $CHCl_3$) (Found: C, 52·4; H, 4·3; N, 6·7; OMe, 14·9%).

(*c*) The D-glyceraldehyde diethyl acetal was isolated from dehydro*seco*vitexin according to method (*b*) and converted into the *di*-p-*nitrobenzoate* of D-glyceraldehyde diethyl acetal which separated from methanol in clusters of needles, m. p. 97·5—98° (Found, in a specimen dried in a vacuum at 80°; C, 54·4; H, 5·0. $C_{21}H_{22}O_{10}N_2$ requires C, 54·5; H, 4·8%).

In the course of exploratory experiments DL-glyceraldehyde dimethyl and diethyl acetate were prepared and converted into the respective di-*p*-nitrobenzoates. The *di*-p-*nitrobenzoate* of the dimethyl acetal separated from methanol or ligroin (b. p. 100—120°) in clusters of needles, m. p. 82—83° [Found: C, 52·8; H, 4·1; N, 6·9; OMe, 14·0. $C_{17}H_{12}O_8N_2(OMe)_2$ requires C, 52·5; H, 4·2; N, 6·5; OMe, 14·3%]. The *di*-p-*nitrobenzoate* of the diethyl acetal formed needles, m. p. 117°, from ligroin [Found: C, 54·5; H, 4·6; N, 6·4; OEt, 19·3. $C_{17}H_{12}O_8N_2(OEt)_2$ requires C, 54·5; H, 4·8; N, 6·1; OEt, 19·5%].

Degradation of Di-O-methylapovitexin.—This compound (0·5 g.) in water (100 ml.) was treated with a solution of sodium metaperiodate (0·32 g.) in water (50 ml.). Next day the solution, which gave a negative reaction with starch–iodide paper, was concentrated in a vacuum, treated with twice its volume of acetone, filtered, and again concentrated. The concentrate was evaporated with the addition of benzene–acetone, and a solution of the residue in benzene containing a little acetone and ethyl acetate was decanted from a little insoluble material and kept at room temperature for five days. *Dehydrodi-O-methylsecoapovitexin* gradually separated in prisms (0·34 g.), m. p. 155—158° with sintering at *ca.* 145° and on recrystallisation from benzene–acetone–ethyl acetate–methanol (10 : 7 : 3 : 6) formed needles which on being heated softened to a translucent gum at 158—159° and then melted with darkening at 179—180°, $[\alpha]_D^{23}$ +30·7° (*c* 1·640 in MeOH) [Found: C, 53·8; H, 5·5; OMe, 18·0. $C_{14}H_{14}O_7(OMe)_2$ requires C, 53·9; H, 5·6; OMe, 17·4%]. In alcohol the compound gave a faint purple ferric reaction which was intensified on the addition of a little water.

Oxidation of Di-O-methylapovitexin with Sodium Metaperiodate in Aqueous Methanol at Room Temperature.—

Experiment 1.				
Time	21 min.	54 min.	70 min.	120 min.
$NaIO_4$, mols.	0·71	1·0	1·11	1·20
Experiment 2.				
Time	8 min.	25 min.	60 min.	180 min.
$NaIO_4$, mols.	1·16	1·46	1·58	1·71

Dehydrodi-*O*-methyl*secoapo*vitexin (0·72 g.) was heated in boiling methanol (32·3 ml.) containing concentrated sulphuric acid (0·82 ml.) for ¾ hr. and the cooled solution poured into a mixture of methanol (100 ml.), water (25 ml.), and barium carbonate (4 g.). The filtered mixture was evaporated in a vacuum, leaving a solid (0·31 g.), m. p. 95—100°, which on purification from benzene or aqueous methanol gave the *dimethyl acetal* of 3-acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde in pale yellow needles, m. p. 114—116°, having a purple ferric reaction in alcohol [Found: C, 59·2, 59·3, 59·4; H, 7·4, 7·5, 7·1; OMe, 42·1, 43·1, 42·9. $C_{10}H_8O_2(OMe)_4$ requires C, 59·1; H, 7·1; OMe, 43·6%]. This product was accompanied by pyruvaldehyde which was isolated as the bis-2 : 4-dinitrophenylhydrazone.

UNIVERSITY OF LIVERPOOL. [*Received, March 30th*, 1957.]

[16] Fischer and Baer, *J. Biol. Chem.*, 1937, **128**, 466.

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697. *The Depolymerisation of Paraldehyde in Ethanol–Water Mixtures. The H_0 Acidity Function in this Solvent.*

By D. P. N. Satchell.

Acidity-function data are presented for solutions of hydrochloric acid in 24·4 moles % ethanol–water up to a concentration of 6·20M. Their usefulness is discussed. The rate of the acid-catalysed depolymerisation of paraldehyde correlates with the results. This result, together with earlier data, leads to the conclusion that the mixed medium in question is a promising one from the Zucker–Hammett viewpoint.

The rate of the acid-catalysed iodination of acetone in a 24·4 moles % ethanol–water solvent is determined[1] much more nearly by the stoicheiometric acid concentration than by the H_0 acidity function[2] for the medium as measured by the base *p*-nitroaniline. This behaviour is the same as that found in water and, if we follow Zucker and Hammett's arguments,[3] is that expected from the known mechanism of the reaction. This being so, a 24·4 moles % ethanol–water mixture seemed likely to prove, in contrast to more ethanolic media,[1] a suitable solvent in which to conduct experiments of the Zucker–Hammett design, which distinguish between different acid-catalysed reaction mechanisms according to whether the reaction rate is determined by the stoicheiometric acid concentration or by the value of H_0 for the medium. The limited H_0 data available for this solvent were therefore extended, and experiments conducted to discover whether a reaction rate known to parallel H_0 in water also did so in the ethanolic mixture. The reaction chosen in the latter connection was the acid-catalysed depolymerisation of paraldehyde.[4]

Experimental

Materials.—" AnalaR " ethanol was used. The concentrated aqueous hydrochloric acid was the B.D.H. reagent, suitable for analysis. The paraldehyde was a redistilled sample, b. p. 124°. *o*-Nitroaniline and 4-chloro-2-nitroaniline were recrystallised samples with m. p. 70·5° and 116° respectively. The alcohol–water–acid mixtures were made up from amounts calculated to keep the ethanol–water ratio constant.

Acidity-function Measurements.—Values of H_0, as measured by the indicator *p*-nitroaniline, for 24·4 moles % ethanol–water containing hydrochloric acid in concentrations up to *ca.* 2·4M have been reported.[1] These data were extended by similar measurements with the indicators *o*-nitroaniline and 4-chloro-2-nitroaniline at *ca.* 18°. The results (see discussion) are given in Table 1 and plotted against the stoicheiometric acid concentration in Fig. 1, which also contains the data for aqueous solutions.

Table 1. *Acidity function in 24·4 moles % ethanol–water as determined by* (*a*) p-*nitroaniline*, (*b*) o-*nitroaniline*, *and* (*c*) 4-*chloro-2-nitroaniline.*

HCl (M)	0·047	0·141	0·430	0·950	1·44	1·90	2·37	3·51	4·39	5·80	6·20
H_0 (by *a*)	2·45	1·95	1·36	0·85	0·51	0·25	−0·02				
H_0 (by *b*)	—	—	(1·29)	0·84	0·51	0·25	0·01	−0·59	−1·07	—	—
H_0 (by *c*)	—	—	—	—	—	0·26	−0·01	−0·59	−1·06	−1·79	−2·10
H_0 (aver.)	2·45	1·95	1·36	0·85	0·51	0·25	−0·01	−0·59	−1·07	−1·79	−2·10

Kinetics of the Depolymerisation of Paraldehyde.—The reaction was followed by a titration method[5] similar to that used by Bell and Brown.[4] A particular acidic medium (*ca.* 80 ml.) was placed in a 100 ml. stoppered flask and the flask and contents brought to 25° in a thermostat bath. The reaction was started by adding a small (*ca.* 0·2 ml.) known quantity of paraldehyde.

[1] Satchell, *J.*, 1957, 2878.
[2] Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940.
[3] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.
[4] Bell and Brown, *J.*, 1954, 774.
[5] Friedemann, Contonio, and Shaffer, *J. Biol. Chem.*, 1927, **73**, 342.

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At appropriate intervals 5 ml. samples were withdrawn and run into sufficient cooled aqueous 5N-sodium hydroxide almost to neutralise the acid, thus stopping the reaction. An excess (*ca.* 15 ml.) of concentrated (0·5M) sodium hydrogen sulphite was now added to convert the free acetaldehyde into its bisulphite compound. After not less than 15 min., during which the vessel was kept tightly corked, most of the excess of hydrogen sulphite was removed with a concentrated iodine solution and the rest with *ca.* N/30-iodine (starch indicator). Just enough sodium hydrogen carbonate to decolorise the indicator was added and the liberated hydrogen sulphite was titrated with standard (*ca.* N/30) iodine. (The use of too much hydrogen carbonate causes the iodine to react with the liberated acetaldehyde.) By this method the infinity titres corresponded to about 97% completion of the reaction.

TABLE 2. *First-order rate constant k for depolymerisation of paraldehyde at 25°.*

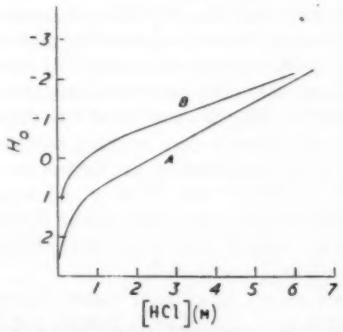
HCl (M)	3·51	2·37	1·90	1·44	0·95	0·43
10^4k (sec.$^{-1}$)	24·8	5·52	3·50	1·61	0·63	0·19

The rate of depolymerisation was measured at six different acidities covering the range 0·43—3·51M-hydrochloric acid. In all cases the first-order plots were linear over at least the first 70% of the reaction. The first-order constants are collected in Table 2.

DISCUSSION

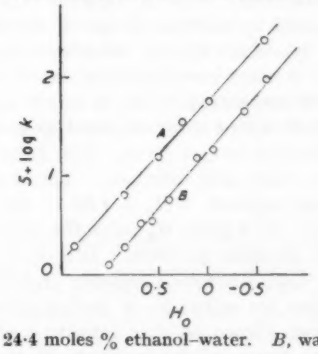
Table 1 shows that in the regions where the data for the different indicators overlap there is good agreement between the measured H_0 values. H_0 values given by *p*-nitroaniline were derived [1] by assuming that the pK_a value for that indicator is 0·99 (the value in water [6]). To obtain the agreement shown in Table 1 it is then necessary to take the pK_a values for *o*-nitroaniline and 4-chloro-2-nitroaniline to be −0·37 and −1·26 respectively, whereas the " best " values drawn by Long and Paul,[6] mainly from data concerning aqueous media, are −0·29 and −1·03 respectively.

FIG. 1. *Acidity functions for hydrochloric acid solutions.*



A, 24·4 moles % ethanol–water. *B*, water.

FIG. 2. *Depolymerisation of paraldehyde.*



A, 24·4 moles % ethanol–water. *B*, water.[4]

These facts imply that on moving from an infinitely dilute solution of acid in water to an infinitely dilute solution of acid in the alcohol–water medium, the values of pK_a for the different indicators (B) change by different amounts, but that for variation of the acid concentration in the ethanolic medium the various activity-coefficient ratios f_B/f_{BH^+} change to roughly the same extent.

For a given indicator,

$$(pK_a^B)_S - (pK_a^B)_W = \log f_B^0.f_{H^+}^0/f_{BH^+}^0 = \Delta pK_a^B \quad . \quad . \quad . \quad (1)$$

[6] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.

where the activity coefficients represent their limiting values at infinite dilution in the solvent S relative to their values at infinite dilution in water (W). Also in the solvent S for any two indicators B and C,

$$(pK_a^C)_S - (pK_a^B)_S = \log [CH^+]/[C] - \log [BH^+]/[B] - \log [(f_C \cdot f_{BH^+})/(f_{CH^+} \cdot f_B)] \quad . \quad . \quad . \quad . \quad (2)$$

The H_0 scale is defined by the equation

$$H_0 = (pK_a)_W - \log [BH^+]/[B] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If the ΔpK_a values for a series of indicators are the same, and if the variation of the ratios of the type f_B/f_{BH^+} with acid concentration is the same for them all in solvent S, then the activity-coefficient term in equation (2) vanishes and the usual stepwise calculation [2] will produce pK_a values equal to those in water, if the calculation is started from an aqueous value. In this case also, H_0 values obtained from eqn. (3) will imply the same amount of ionisation as they do in water and values calculated for different indicators will overlap exactly.

If, however, the ΔpK_a values for a series of indicators are not the same, then even if terms such as f_B/f_{BH^+} should vary with acidity in solvent S in the same way, the activity-coefficient term in eqn. (2) will not vanish, but will be constant for each pair of indicators. Hence a stepwise calculation of pK_a based on a given aqueous value as a starting point will not reproduce the aqueous pK_a values for the rest of the sequence. Also H_0 values calculated from eqn. (3) will not coincide where data for successive indicators overlap. To make them do so a constant must be added, as here found. Such circumstances are envisaged by Gutbezahl and Grunwald [7] when they state that the H_0 scale as defined in eqn. (3) will not exist in some solvents. This fact, however, does not defeat the usefulness of the concept provided that terms such as $f_C \cdot f_{BH^+}/f_{CH^+} \cdot f_B$ remain constant with changes in acid concentration for, if this is so, then appropriate acid-catalysed reaction rates will correlate with values obtained as were those in Table 1. Fig. 2 shows that the data for paraldehyde in fact do so. Fig. 2 also contains Bell and Brown's data refering to aqueous hydrochloric acid solutions. The slope of the plot of the logarithm of the first-order rate constant against $-H_0$ is 1·09 in the mixed solvent compared with 1·16 in the aqueous media. At a given H_0 value the reaction rate in water is about three-fold slower than that in the alcoholic medium. This discrepancy is probably mainly due to the inconstancy of ΔpK_a values between aqueous and ethanolic media already mentioned.

Thus for solutions of hydrochloric acid in a 24·4 moles % ethanol–water solvent it has been shown (*a*) that activity-coefficient ratios such as $f_C \cdot f_{BH^+}/f_{CH^+} \cdot f_B$ remain constant for the three indicators used, (*b*) that a reaction rate known to depend on the acidity function behaves in the expected manner, and (*c*) that a reaction rate known to depend on the hydrogen-ion concentration in aqueous media continues to follow this concentration fairly accurately in the mixed solvent.[1] Hence this particular ethanol–water mixture seems a promising medium from the Zucker–Hammett viewpoint.

KING'S COLLEGE, STRAND, W.C.2. [*Received, March 27th,* 1957.]

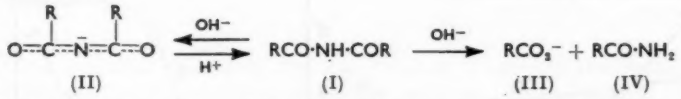
[7] Gutbezahl and Grunwald, *J. Amer. Chem. Soc.*, 1953, **75**, 559, 565.

698. *The Hydrolysis of Amides and Related Compounds. Part IV.* Diacetylamine and Succinimide in Aqueous Alkali.*

By J. T. Edward and K. A. Terry.

The rates of hydrolysis of diacetylamine and succinimide in alkaline solution are proportional to the fraction of the imide ionized, and not to the concentration of hydroxide ion. These results are explicable by a mechanism in which the rate-determining step is the reaction of a hydroxide ion with an un-ionized molecule of imide. Some misinterpretations in the literature are indicated.

The alkaline hydrolysis of the imide grouping (AH; I) is of interest in connection with recent procedures for peptide degradation.[1] While kinetic studies have been made of the hydrolysis (I ⟶ III + IV) of some linear [2] and cyclic imides,[3,4] no attention has been paid to the effect of ionization: AH ⟶ A^- (II) + H^+, on the rate of hydrolysis. From analogy with the alkaline cleavage of several other ionizable compounds,[5,6] the ionized imide (II) should be resistant to alkaline hydrolysis, and this should affect the kinetics of the reaction.



(II) (I) (III) (IV)

Accordingly, we have measured the ionization constants and rates of hydrolysis of diacetylamine (I; R = Me) and succinimide (I; RR = $[CH_2]_2$), by spectrophotometric methods. Diacetylamine [7] and succinimide [8] show weak absorption in neutral solution, but greatly enhanced absorption in alkali,[9] with $\lambda_{max.}$ at 240 mμ and at <222 mμ, respectively. Since solutions of both materials at low concentrations obey Beer's law,[7,8] we have used the variation in absorption with pH to determine the ionization constants of the compounds,[10] and the progressive decrease in absorption on storage to follow their hydrolysis.

Experimental

Materials and Apparatus.—Diacetylamine,[11] acetamide, succinimide, and succinamic acid [12] were recrystallized to constant m. p. Aqueous sodium hydroxide of different concentrations was used for obtaining the pH range 11·5—14; and phosphate or borate buffer solutions for lower pH's. The pH values of all solutions were determined potentiometrically, a Radiometer pH meter 23 being used, with glass and calomel electrodes, before and after hydrolysis; since in most cases the ionic strength of the solution was small (~0·02M), it may be assumed that $pH \approx -\log[H^+] \approx -\log K_w/[OH^-]$, K_w being the ionic product of water.[10] Absorption measurements were made with a Beckman DU spectrophotometer on solutions in 1-cm. quartz cells, kept at 25·00° ± 0·02° by circulating water in the cell carrier.[13]

Rate Measurements.—(*a*) *Diacetylamine.* Aqueous solutions of diacetylamine (10^{-4}—5×10^{-3}M)

* Part III, *J.*, 1957, 2009.

[1] Battersby and Robinson, *J.*, 1955, 259.
[2] Titherley and Stubbs, *J.*, 1914, **105**, 299; Desai and Desai, *J. Indian Chem. Soc.*, 1951, **28**, 99.
[3] Ingold, Sako, and Thorpe, *J.*, 1922, **121**, 1177.
[4] Sircar, *J.*, 1927, 600, 1252.
[5] Goldschmidt and Oslan, *Ber.*, 1899, **32**, 3390; 1900, **33**, 1140; Hauser, Swamer, and Ringler, *J. Amer. Chem. Soc.*, 1948, **70**, 4023; Gustafsson and Johanson, *Acta Chem. Scand.*, 1948, **2**, 42.
[6] Pearson and Mayerle, *J. Amer. Chem. Soc.*, 1951, **73**, 926; Pearson and Sandy, *ibid.*, p. 931.
[7] Polya and Spotswood, *Rec. Trav. chim.*, 1949, **68**, 573.
[8] Saidel, *Nature*, 1953, **172**, 955.
[9] Cf. Stuckey, *J.*, 1947, 331.
[10] Gold, "pH Measurements," Methuen, London, 1956, p. 90.
[11] Dehn, *J. Amer. Chem. Soc.*, 1912, **34**, 1399.
[12] Geoffrey and Vogel, *J.*, 1934, 1103.
[13] Campbell and Simpson, *Chem. and Ind.*, 1953, 887.

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and of sodium hydroxide or buffer solution (2·00 ml.), each at 25·00° ± 0·02°, were mixed in a quartz cell, and the absorption at 240 mμ measured as soon as possible, and at intervals thereafter; from these values the molar extinction coefficients ε_t at different times t were calculated. In strongly alkaline solution the absorption quickly approached zero, as would be expected for the reaction (I; R = Me) ⟶ (III; R = Me) + (IV; R = Me), since an aqueous solution of acetamide and sodium acetate has a total extinction $\varepsilon = 5$ at 240 mμ. Plots of log ε_t against t gave straight-line curves (*e.g.*, Fig. 1), from the slopes of which the apparent first-order rate constants k_e for the hydrolysis of the imide were calculated (see Table). From the graphical data of Titherley and Stubbs,[2] diacetylamine has a half-life of about 25 sec., or an apparent first-order rate constant $k_e \approx 0{\cdot}028$ sec.$^{-1}$, in 2 equivalents of 0·1N-sodium hydroxide at room temperature, *i.e.*, in a solution of pH 12·9 changing to pH 12·7 during the reaction (since for diacetylamine $pK'_a = 12{\cdot}9$: see below). This is in rough agreement with our values for this pH range.

(*b*) *Succinimide.* Hydrolysis was followed by the change in ε_t of 0·01—0·001M-solutions at 235 mμ, the molar extinction coefficient (= 35) of succinamic acid being taken as ε_∞. The hydrolysis of succinamic acid in alkaline solution was found to lead to a further drop in absorption,

FIG. 1. *Hydrolysis of diacetylamide at* pH 11·94 (*curve a*) *and* 13·52 (*curve b*).

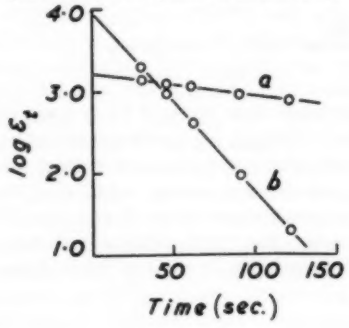
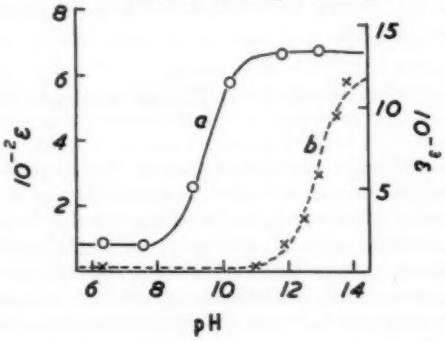


FIG. 2. *Variation of absorption with* pH.



	Theory	*Exptl.*
Left-hand scale: succinimide at 235 mμ ...	*a*	o
Right-hand scale: diacetylamine at 240 mμ...	*b*	x

but was so slow in comparison with the hydrolysis of succinimide that it could be ignored. Plots of log $(\varepsilon_t - \varepsilon_\infty)$ against time gave satisfactory straight-line curves, from which values of k_e (see Table) were obtained. Sircar [4] followed by titration the hydrolysis of succinimide by hydroxide ion (both initially 0·005M) but failed to take account of the neutralization reaction. The pH of this solution should change from about 10·6 to 10·2 in going from 0 to 80% hydrolysis, and k_e should drop from 93 to 83% of the maximum value (see below), attained in more alkaline solutions. A replotting of Sircar's results gives $k_e = 3{\cdot}73 \times 10^{-3}$ sec.$^{-1}$, in poor agreement with our results for this pH range.

Dissociation Constants.—The values of the extinction coefficients ε of the imides in solutions of different pH, before any hydrolysis, were obtained from the intercepts of their rate curves (*e.g.*, Fig. 1) with the abscissæ, and are given as points in Fig. 2. It is evident that the points fit reasonably well the theoretical curves for the equation [10]

$$\mathrm{pH} = pK'_a + \log (\varepsilon - \varepsilon_u)/(\varepsilon_i - \varepsilon)$$

where ε_u is the molar extinction coefficient of the un-ionized imide, ε_i of the ionized imide, ε of a mixture of un-ionized and ionized molecules at the indicated pH, and pK'_a is defined by $pK'_a = \mathrm{pH} - \log\{[A^-]/[AH]\}$. In plotting the theoretical curves, pK'_a's of 9·5 and 12·9 have been assumed for succinimide and diacetylamine, and $\varepsilon_i = 12{,}100$ at 240 mμ for diacetylamine. Thermodynamic-dissociation index values pK_a [$= \mathrm{pH} - \log\{(A^-)/(AH)\}$, the quantities in parentheses being activities] of 9·560 and 9·656 have been reported [14, 15] for succinimide.

[14] Simms, *J. Phys. Chem.*, 1928, **32**, 1121.
[15] Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.

Results and Discussion

The apparent first-order rate constant k_e for the hydrolysis of a simple amide in an excess of alkali is proportional to the hydroxide-ion concentration.[16] However, the rate constants for the hydrolysis of diacetylamine and succinimide are not proportional to the concentration of hydroxide ion, but, within the limits of experimental error, to the fraction α of imide ionized, where $\alpha = [A^-]/([AH] + [A^-]) = K'_a/([H^+] + K'_a)$ (see Table).

First-order rate constants (k_e) for hydrolysis at different pH's.

Diacetylamine

pH	11·94	12·52	12·95	13·52	13·83
10^2k_e (sec.$^{-1}$)	0·64	2·03	4·10	5·07	7·50
$10^2k_e/\alpha$ [a]	6·0	6·9	7·7	6·3	8·4
$k_e/[OH^-]$	0·68	0·61	0·46	0·15	0·11

Succinimide

pH	9·11	10·24	11·90	13·00
10^4k_e (sec.$^{-1}$)	0·31	0·81	1·02	0·95
$10^4k_e/\alpha$ [b]	1·09	0·96	1·02	0·95
$k_e/[OH^-]$	2·4	0·47	0·013	0·001

[a] Assuming $pK'_a = 12·9$. [b] Assuming $pK'_a = 9·5$.

The kinetic results are consistent with the assumption that the rate-determining step in the hydrolysis is the attack of the un-ionized imide by a hydroxide ion. The rate of hydrolysis v will then be given by

$$v = k_2[AH][OH^-] = k_2K_w[A^-]/K'_a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k_2 is a second-order rate constant. Since k_e is based on the change in stoicheiometric concentration of imide, ionized and unionized,

$$v = k_e([A^-] + [AH])$$

$$\text{or } k_e = k_2K_w[A^-]/K'_a([A^-] + [AH]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

$$= k_2K_w\alpha/K'_a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2b)$$

On the basis of this mechanism, succinimide is more stable than diacetylamine to alkaline hydrolysis chiefly because of its greater acidity. Thus it is hydrolysed 710 times more slowly than diacetylamine at pH 11·9; at this pH it is 99·6% ionized to the unreactive form, while diacetylamine is only 12·1% ionized. The stabilities, if given in terms of the k_2 values in equations (1) and (2) rather than the k_e values, are of the same order of magnitude. Similar considerations apply to the alkaline hydrolysis of glutarimide, reported by Sircar [4] to be more rapid than that of succinimide, and explained on theoretical grounds.[17] In fact, analysis of Sircar's data in terms of equation (2), the reported [15] dissociation constant ($pK_a = 11·43$) of glutarimide being used, indicates the un-ionized molecule to be hydrolyzed about five times more slowly than the un-ionized molecule of succinimide, although the drift in pH during the hydrolysis makes the calculation only very approximate. Other kinetic work [2,3] on imide hydrolysis requires similar revision.

The differences in the acid dissociation constants of the imides are probably the result of conformational differences.[18] Thus with diacetylamine, the planar amide linkage [19] restricts the conformations of the molecule to (Va), (Vb), and (Vc). The first conformation, in which diacetylamine would have two *cis* amide linkages like succinimide, is

[16] Reid, *Amer. Chem. J.*, 1899, **21**, 284; 1900, **24**, 397; Meloche and Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.
[17] Brown, Brewster, and Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.
[18] Cf. Hesse and Krehbiel, *Annalen*, 1955, **593**, 35.
[19] Pauling, Corey, and Branson, *Proc. Nat. Acad. Sci.*, 1951, **37**, 205.

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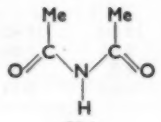
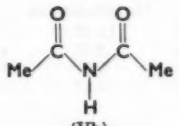
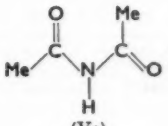
improbable because of steric repulsions between the two methyl groups.[20,21] These repulsions would be at a minimum in the extended form (Vb), which seems most probable. However, the formation of the anion (II; R = Me) corresponding to conformation (Vb) would create large electrostatic repulsions between the neighbouring carbonyl oxygens,[20] on which much of the negative charge would be localized, and hence formation of this ion would be expected to take place less readily than the formation of the ion (II; R = $[CH_2]_2$) from succinimide. The weak acidity of glutarimide [15] may be caused by a lack of planarity in one of the amide linkages due to ring buckling; this will hinder the charge delocalization necessary in forming the ion (II; RR = $[CH_2]_3$).


(Va)


(Vb)


(Vc)

In solutions 2 or more pH units above pH = pK'_a, α approaches unity, and k_e approaches a maximum value. Hence the most selective fission of a succinimide ring in the presence of peptide linkages (*e.g.*, ref. 1) will be achieved at pH's below about 9.

We are grateful to Dr. J. C. P. Schwarz for much advice and discussion, to Professor Cocker for constant encouragement, and to Imperial Chemical Industries Limited (General Chemicals Division) for a research grant (to K. A. T.).

TRINITY COLLEGE, DUBLIN. [*Received, April 4th*, 1957.]

[20] Calvin and Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 3152.
[21] Forbes and Mueller, *Canad. J. Chem.*, 1955, **33**, 1145.

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699. *Immunopolysaccharides. Part VI.* The Isolation and Properties of the Dextransucrase of* Betacoccus arabinosaceous.

By R. W. BAILEY, S. A. BARKER, E. J. BOURNE, and M. STACEY.

The isolation and properties of a cell-free dextransucrase preparation from *Betacoccus arabinosaceous* (Birmingham strain) is described. This preparation, which contains pre-formed dextran, is shown to contain two enzymes which together synthesise a branched dextran. Partial destruction of one of the enzymes yields a preparation which will then only synthesise a relatively unbranched dextran.

IN 1941, Hehre [1] described the isolation, from cultures of *Leuconostoc mesenteroides*, of a heat-labile cell-free extract, which synthesised from sucrose a polysaccharide indistinguishable from a dextran by certain chemical and serological tests. He postulated that the synthesis, catalysed by dextransucrase, proceeded according to the equation:

$$n \text{ Sucrose} \longrightarrow (\text{Glucose})_n + n \text{ Fructose}$$

Improvements in the method of isolation by precipitation with chloroform [2] and ammonium sulphate [3] were later reported. The use of ethanol and ammonium sulphate has also been mentioned,[4] without experimental details. The purpose of this and the succeeding communication is to report the progress of attempts to isolate, purify, and free from pre-formed dextran the enzymes responsible for the synthesis of the linear (α-1 : 6) and branched

* Part V, *J.*, 1955, 2096.

[1] Hehre, *Science*, 1941, **93**, 237.
[2] Hehre and Sugg, *J. Exp. Med.*, 1942, **75**, 339.
[3] Hehre, *J. Biol. Chem.*, 1946, **163**, 221.
[4] Koepsell, Tsuchiya, Hellmann, Kazenko, Hoffmann, Sharpe, and Jackson, *ibid.*, 1953, **200**, 793.

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(α-1 : 3) portions of structures of dextrans elaborated by *Betacoccus arabinosaceous* (Birmingham strain).[5, 6]

A standard method of isolating a highly active dextransucrase from the cell-free culture of *B. arabinosaceous* was devised using precipitation at 0° with 35% ethanol and reprecipitation at 0° with 25% ethanol. Although control experiments had shown that in protein-free solution no dextran fraction normally elaborated by *B. arabinosaceous* was precipitated with 25% ethanol (v/v) at 0°, the presence of dextransucrase appeared to cause the formation of a dextran–dextransucrase complex which was precipitable under these conditions. The dextran content of three freeze-dried enzyme preparations, isolated by this method, varied from 71·4 to 81·4%.

The assay of enzyme activity was carried out by a method similar to that used by Koepsell *et al.*[4] except that the digest was incubated at 25° instead of 30°. A tenfold increase in the amount of sucrose present in the digest caused an apparent doubling in the activity of the enzyme as measured by the total amount of fructose produced (Table 1, p. 3533). The enzyme preparation was free from any enzyme which attacked the fructose formed during dextran synthesis and its activity was not affected appreciably by the amount of acetate buffer (pH 5·0) used (Table 2). In determining enzyme activity prolonged incubation (>20 hr.) was avoided since in the later stages there was a decrease in the rate of fructose production due to the decreased amount of sucrose present and the appreciable inhibition of the enzyme reaction by large amounts of fructose (see below). The optimum pH of dextransucrase activity was *ca.* 5·5 and the optimum temperature *ca.* 29°; the enzyme exhibited little activity above pH 7·0 and 36°.

Many unsuccessful attempts were made to free the enzyme preparation from pre-formed dextran. Fractionation by ammonium sulphate always gave inactive preparations; paper chromatography at 0° in various concentrations of aqueous acetone or aqueous ethanol did not separate enzyme activity and pre-formed dextran. No absorption could be detected on cellulose powder suspended in a buffered solution (pH 6·0) of the enzyme. All activity was readily absorbed on charcoal from which, however, it could not be eluted by water, 0·1M-citrate buffer (pH 6·0) or 0·1M-acetate buffer (pH 6·0). Shaking with chloroform at 0° by a method similar to that of Hehre and Sugg [2] gave an inactive precipitate. Reprecipitation with ethanol, although giving an active enzyme, did not remove any appreciable proportion of dextran. To avoid carrying these experiments out on the larger scale, necessary for the determination of the amount of dextran present by acid hydrolysis, each enzyme fraction was tested in the presence and absence of added dextran. This was done in the belief that dextransucrase, free from pre-formed dextran, would, like muscle phosphorylase, only exhibit full activity in the presence of added primer (in this case dextran).

The standard dextransucrase preparation, when freshly freeze-dried, synthesised a highly branched dextran which showed high optical rotation ($[\alpha]_D$ +217°), was converted into glucose by acid hydrolysis to the extent of 101%, contained <0·1% of fructose, and showed an infrared spectrum similar to the highly branched dextran normally produced by *Betacoccus arabinosaceous*.[5] After storage at 0° for 2 months, the same enzyme preparation synthesised a dextran showing a lower optical rotation ($[\alpha]_D$ +190°) and although obtained in approximately the same degree of purity (% conversion into glucose, 96; fructose content <0·1%) gave an infrared spectrum similar to the modified relatively unbranched dextran elaborated by *Betacoccus arabinosaceous* in a magnesium-deficient medium.[6] These results were confirmed by periodate oxidation and the amounts of glucose detectable in the hydrolysates of the periodate-oxidised dextrans. It is concluded that the standard dextransucrase preparation contains two enzymes, one of which is responsible for the synthesis of α-1 : 6-links, and another which is responsible for the formation of the α-1 : 3-branch points.

[5] Barker, Bourne, Bruce, Neely, and Stacey, *J.*, 1954, 2395.
[6] Barker, Bourne, James, Neely, and Stacey, *J.*, 1955, 2096.

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In 1953, Koepsell *et al.*[4] showed that certain simple sugars could act as chain-initiators when the dextransucrase of *Leuconostoc mesenteroides* (NRRL B-512) acted on sucrose. This observation was also found to apply to the dextransucrase of *Betacoccus arabinosaceous*.[7] Isomaltose, maltose, and methyl α-D-glucoside caused marked increases in the amounts of fructose produced by dextransucrase from sucrose owing to their ability to act as alternative acceptors. The actual increase, although constant for a given enzyme preparation, varied with each batch of enzyme, owing no doubt to the amount and nature of preformed dextran already present in the enzyme. D-Glucose and polygalitol exhibited a less marked effect on fructose production, while the effects of D-galactose, lactose, melibiose, and cellobiose although detectable varied with the batch of enzyme taken. Fructose caused a decrease in the amount of fructose produced whichever batch of enzyme was taken (see Table 6).

The presence of isomaltose, maltose, and D-glucose caused a marked decrease in the amount (and probably molecular size) of dextran produced and each led to the synthesis of a series of oligosaccharides. Some of these oligosaccharides (isomaltotriose, panose, isomaltose, etc.) were of known constitution and contained the added sugar incorporated at the reducing end, together with a series of glucose units in α-1 : 6-linkage at the non-reducing end. Cellobiose, lactose, D-galactose, and methyl α-D-glucoside also gave series of oligosaccharides. The structures of trisaccharides obtained from cellobiose and lactose have been recently described,[8,9] and both were found to be formed by the addition of a glucose unit in α-1 : 2-linkage to the reducing moiety of the disaccharide. It is believed that some of the sugars in Table 8 (*e.g.*, maltose more than glucose) have the ability to desorb the enzyme from the dextran–dextransucrase complex, making it more effective and causing an increase in fructose production. The sugars then act either as alternative acceptors (*e.g.*, maltose) or competitive inhibitors (*e.g.*, fructose). It is realised that one anomer, *e.g.*, α-D-glucopyranose, might differ in these properties from the other anomer, *e.g.*, β-D-glucopyranose, particularly in view of the totally different behaviour of maltose and cellobiose.

Although these initial experiments did not produce a dextransucrase free from dextran they did suggest a method of obtaining such an enzyme by growing the bacteria on sucrose in the presence of large amounts of maltose and so providing a source in which the enzyme is accompanied by only traces of the polysaccharide. They also provided evidence of the presence of at least two enzymes concerned in the synthesis of branched dextrans.

Experimental

Standard Method of Isolation of Dextransucrase.—An aqueous medium (4 l.), containing yeast extract (1%), $Na_2NH_4PO_4$ (0·5%), KH_2PO_4 (0·1%), $MgSO_4.7H_2O$ (0·05%), and sucrose (10%), was adjusted to pH 7 with sodium hydroxide and steam-sterilised at 15 lb./sq. in. for 30 min. After inoculation from an actively growing culture of *Betacoccus arabinosaceous* (Birmingham strain) it was incubated at 25° for 17 hr. The culture (pH 6·6) was cooled to 0° and ethanol (2160 ml.; final concentration 35% v/v) added slowly with stirring. Care was taken to maintain the temperature at 0—1° throughout this and all the following procedure. After 1 hr., a dark gummy precipitate was recovered by centrifuging (2000 r.p.m.), dissolved in 0·1M-citrate buffer (500 c.c.; pH 6·0), and centrifuged at 5000 r.p.m. for 30 min. to give a cell-free enzyme solution. 0·1M-Citrate buffer (2500 c.c.; pH 6·0) was then added to give a solution containing approximately 1·5 units of activity/c.c. The dextransucrase was isolated from this solution by dissolving in water (200 c.c.) the precipitate produced overnight by the addition of ethanol (1 l.; final concentration 25% v/v). After clarification by centrifuging at 5000 r.p.m. the supernatant solution was freeze-dried and stored at 0° as a brown powder (4·06 g.). Several batches of enzyme were prepared.

Standard Method for the Determination of Dextransucrase Activity.—The enzyme (100 mg.)

[7] Bailey, Barker, Bourne, and Stacey, *Nature*, 1955, **175**, 635.
[8] *Idem, ibid.*, **176**, 1164.
[9] Barker, Bourne, Grant, and Stacey, *ibid.*, 1956, **178**, 1221.

was dissolved in 0·05M-acetate buffer (30 c.c.; pH 5·0), and the solution centrifuged (5000 r.p.m.) for 30 min. A portion (2 c.c.) was pipetted into a 25 c.c. standard flask, and freshly prepared sucrose solution (300 mg. in 3 c.c. of 0·05M-acetate buffer, pH 5·0) added. This digest was incubated at 25° for 3 hr. together with two blank digests containing respectively (*a*) enzyme solution (2 c.c.) and 0·05M-acetate buffer solution, pH 5·0 (3 c.c.), and (*b*) sucrose (300 mg.) in 0·05M-acetate buffer, pH 5·0 (5 c.c.). Each solution was then neutralised by 0·25N-sodium hydroxide (phenol-red). Iodine solution (2 c.c.; iodine, 8·7 g., and potassium iodide, 16·7 g. per l.) was added followed by 0·175N-sodium hydroxide (1 c.c.). Each flask was shaken, stoppered, and left for 10 min. at room temperature. After acidification with 0·25N-sulphuric acid (1 c.c.), the excess of iodine was removed with 0·02—0·04N-sodium sulphite, starch glycollate being used as an indicator. Each solution was neutralised with 0·25N-sodium hydroxide and diluted to 25 c.c. The fructose present in an aliquot part (5 c.c.) of each solution was then determined by the copper reagent of Shaffer and Hartmann.[10] A unit of dextransucrase activity is that required for the complete conversion of 1 mg. of sucrose into dextran and fructose in 1 hr. at 25° provided that not more than one-half of the sucrose present has been utilised.

Effect of Sucrose Concentration on Dextransucrase Activity.—The activity of a freeze-dried dextransucrase preparation (2 c.c. portions) was measured by the standard method except that differing amounts of sucrose, each dissolved in 0·05M-acetate buffer (3 c.c.; pH 5·0), were used in a series of digests. The results are given in Table 1.

TABLE 1. *Effect of sucrose concentration on enzyme activity.*

Sucrose added (mg.)	30	50	70	100	300	500
Fructose produced (mg.)	2·21	2·38	2·86	3·26	4·53	4·60
Apparent activity (units/2 c.c.)	1·40	1·51	1·81	2·06	2·87	2·91

Effect of Acetate Buffer on Dextransucrase Activity.—The activity of portions (2 c.c.) of the enzyme was determined by the standard method except that the volume of the 0·05M-acetate buffer (pH 5·0) was varied as in Table 2.

TABLE 2. *Effect of acetate buffer on enzyme activity.*

Volume of buffer (c.c.)	5	8	11
Fructose produced (mg.)	4·70	4·70	4·65

Stability of Fructose in the Presence of Dextransucrase.—Fructose dissolved in 0·05M-acetate buffer (pH 5·0; 2 c.c.) was incubated with the enzyme (2 c.c.) for 20 hr. at 25°. Estimation showed the same amount of fructose (10 mg.) to be present as in a control containing fructose incubated in the absence of the enzyme for 20 hr. at 25°.

Effect of Time of Incubation on Enzyme Activity Determination.—The activity of portions (2 c.c.) of dextransucrase was determined by the standard method except that 10% sucrose–buffer solution (5 c.c.) was used and the digests were incubated for various times (Table 3).

TABLE 3. *Effect of incubation time on activity determination.*

Time of incubation (hr.)	0	3	15	23	48	93
Fructose produced (mg.)	0	6·15	29·75	41·75	51·50	73·50
Apparent activity (units/2 c.c.)	0	3·89	3·77	3·45	2·04	1·50

Effect of pH *on the Activity of Dextransucrase.*—Portions of dextransucrase (100 mg.) were dissolved in 0·05M-acetate buffer (30 c.c.) of various pH values. After being centrifuged for 30 min. at 5000 r.p.m., aliquot parts (2 c.c.) of each solution were mixed with sucrose (300 mg.), dissolved in 0·05M-acetate buffer (3 c.c.) of the same pH, and the enzyme activity measured by the standard method (see Table 4). Control digests omitting (*a*) the enzyme, and (*b*) the sucrose, were also run and gave normal blank titrations.

TABLE 4. *Effect of* pH *on dextransucrase activity.*

pH of acetate buffer	4·0	4·5	5·0	5·5	6·0	6·5	7·0
Apparent activity (units/2 c.c.)	0·47	1·39	1·75	2·19	1·78	1·08	0·58

Effect of Temperature on Dextransucrase Activity.—The activities of portions (2 c.c.) of dextransucrase solution were measured in a series of digests by the standard method except

[10] Shaffer and Hartmann, *J. Biol. Chem.*, 1921, **45**, 377.

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that they were incubated at various temperatures. Those at 1° and 8° were incubated for 20 hr., the remainder were incubated for 3 hr. (see Table 5).

TABLE 5. *Effect of temperature on enzyme activity.*

Temperature	1°	8°	19°	25°	29°	36°
Apparent activity (units in 2 c.c.)	0·30	0·40	1·09	1·75	1·85	0·56

Carbohydrate Content of Dextransucrase.—Freeze-dried enzyme (25 mg.) prepared by the standard method was hydrolysed with 2N-sulphuric acid (2 c.c.) at 100° for 4 hr. The hydrolysate was cooled, neutralised with 2N-sodium hydroxide and diluted to 50 c.c. The % conversion, estimated as glucose by the method of Shaffer and Hartmann,[10] corresponded to 71·4, 76·1, and 81·4% for three enzyme preparations.

Effect of Added Sugars on Dextransucrase Activity.—The activity of dextransucrase was measured by the standard method in the presence of a series of sugars (100 mg. each) which were added to the digests as their solutions in 0·05M-acetate buffer (2 c.c.; pH 5·0). Additional controls, omitting the sucrose or dextransucrase, were carried out in the presence of each added sugar. The digests were incubated for 20 hr. in order to obtain a suitable ratio of fructose to added sugar and after dilution to 25 c.c. the following aliquot parts were used for hypoiodite oxidation and fructose measurement: (i) added reducing monosaccharides, 1 c.c.; (ii) added reducing disaccharides, 2 c.c.; and (iii) added non-reducing sugars, 5 c.c. In the case of reducing sugars with a low priming effect a second fructose measurement was made on a larger aliquot portion (5 c.c.) and an increased amount of alkaline iodine to oxidise the added sugar. Controls showed that the extra iodine did not affect the fructose measurement. Except in the case of added fructose all the control digests gave thiosulphate titrations identical with the blank titration. Table 6 gives the effect of added sugars on two batches of enzyme, (A) containing 0·6 unit/mg. and (B) containing 0·3 unit/mg.

TABLE 6. *Effect of added sugars on dextransucrase activity.*

	Batch A		Batch B	
Added sugar	Fructose (mg.) produced	Change (%) in production	Fructose (mg.) produced	Change (%) in production
None	38·8	—	17·5	—
Isomaltose	86·3	+123	48·2	+175
Maltose	80·0	+107	43·8	+150
Methyl α-D-glucoside	54·3	+ 40	28·0	+ 60
D-Glucose	43·8	+ 13	21·3	+ 21
1-Deoxy-D-glucose	45·0	+ 16	—	—
D-Galactose	39·9	+ 3	18·3	+ 4
Lactose	31·3	− 19	18·5	+ 6
Melibiose	34·4	− 11	18·3	+ 4
Cellobiose	38·8	0	18·5	+ 6
D-Fructose	33·8	− 13	13·8	− 22

Other compounds tested with batch A enzyme and having a negligible effect (<5%) were α-D-glucose 1-phosphate, methyl β-D-glucoside, D-glucuronic acid, D-xylose, L-arabinose, D-mannose, D-glucitol, D-mannitol, inositol, αα-trehalose, laminaribiose, raffinose, and melezitose. Although all the reducing sugars, except isomaltose, were crystalline α- or β-anomers, they would, in solution, have been present through most of the incubation as mixtures of anomers.

Effect of Increasing Amounts of Maltose on the Activity of Dextransucrase.—The effect of varying amounts of maltose on the activity of batch A and batch B enzyme was investigated under the conditions outlined in the previous experiment (see Table 7).

Chromatographic Analysis of Standard Digests containing Added Sugars.—A series of standard dextransucrase digests containing added sugars (100 or 200 mg.) was prepared in the manner previously described and incubated at 25° for 20 hr. Without dilution or addition of hypoiodite, each digest was submitted to paper chromatography in the organic phase of a mixture of butanol (40%), ethanol (10%), water (49%), and ammonia (1%), the papers being sprayed severally with aniline hydrogen phthalate,[11] naphtharesorcinol,[12] and alkaline silver nitrate.[13]

[11] Partridge, *Nature*, 1949, **164**, 443.
[12] Forsyth, *ibid.*, 1948, **161**, 239.
[13] Trevelyan, Proctor, and Harrison, *ibid.*, 1950, **166**, 444.

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For the separation of higher oligosaccharides a more aqueous solvent [14] containing butanol (40), water (20), ethanol (12), and ammonia (1) was used to irrigate the chromatograms. With sugars having reducing glucose or galactose groups the benzylamine–ninhydrin technique [14] was used. Additional evidence was obtained by paper ionophoresis [15] in borate buffer (pH 10). The additional components detected, other than the added sugar, sucrose, fructose, and traces of glucose, are listed in Table 8.

TABLE 7. *Effect of maltose concentration on dextransucrase activity.*

Batch A			Batch B		
Maltose (mg.) added	Fructose (mg.) produced	Increase (%) in fructose	Maltose (mg.) added	Fructose (mg.) produced	Increase (%) in fructose
0	38·8	—	0	17·5	—
10	42·5	10	12·5	22·4	28
20	49·9	29	25	27·0	55
30	55·9	44	50	34·4	97
50	62·1	60	75	39·8	127
100	78·6	103	100	43·8	150
200	90·9	135	200	45·5	160

TABLE 8. *Analysis of standard digests containing added sugars.*

Added sugar	Additional components and probable identities
Isomaltose (100 mg.)	Isomaltotriose, tetra- and penta-saccharides
Maltose (100 mg.)	Panose, tetra- and penta-saccharides
Cellobiose (100 mg.)	Trisaccharide (see ref. 9)
Lactose (200 mg.)	Trisaccharide (see ref. 8)
Melibiose (200 mg.)	None
Methyl α-D-glucoside (200 mg.)	Methyl bioside, methyl trioside
Galactose (200 mg.)	Disaccharide, trisaccharide
Glucose (100 mg.)	Isomaltose, isomaltotriose, isomaltotetraose
Fructose (200 mg.)	None
1-Deoxy-D-glucose (100 mg.)	None

Synthesis of Dextran with Dextransucrase.—Freshly freeze-dried enzyme (100 mg.) was extracted with 0·05M-acetate buffer (pH 5·0; 30 c.c.), and a portion (20 c.c.) mixed with sucrose (4 g.) in 0·05M-acetate buffer (pH 5·0; 40 c.c.). After 5 days at 25°, ethanol (120 c.c.) was slowly added with stirring and the mixture left at 0° overnight. The precipitated dextran was dissolved in water (200 c.c.), boiled for 10 min., then cooled, and the suspension centrifuged to remove coagulated protein. After dialysis against running water for 48 hr. the dextran (0·590 g.), obtained by freeze-drying, was dissolved in water (200 c.c.) and reprecipitated by addition of ethanol (200 c.c.) at 0°. After freeze-drying and drying over phosphoric oxide at 60° *in vacuo* 0·430 g. of dextran (I) was obtained. After the freeze-dried enzyme used above had been stored at 0° for 2 months, a second larger batch of dextran was synthesised under the same conditions, by using enzyme (400 mg.) and sucrose (24 g.) in 0·05M-acetate buffer (pH 5·0; 360 c.c.). The dextran obtained (3·813 g.) was also subjected to reprecipitation from water (600 c.c.) by the addition of ethanol (600 c.c.) at 0°, the yield obtained after drying being 3·553 g. of dextran (II).

Dextran (I) had $[\alpha]_D^{19}$ +217° (*c* 0·22 in N-NaOH) while dextran (II) showed $[\alpha]_D^{19}$ +190° (*c* 0·20 in N-NaOH). After hydrolysis of each dextran (20 mg.) with N-sulphuric acid (2 c.c.) at 100° for 2 hr., neutralisation, and paper chromatography of the hydrolysate, visual comparison of spot intensities with those of fructose subjected to the same treatment indicated that each dextran hydrolysate contained <0·1%.

The conversions of the dextrans into glucose after acid hydrolysis with 1·5N-sulphuric acid at 100° for 5 hr. were 101 and 96%, respectively.

Both dextran (I) and dextran (II) showed infrared absorption peaks at 917 and 768 cm.$^{-1}$ (α-1 : 6-linkages) and at 841 cm.$^{-1}$ (shown by α-anomers in the D-glucopyranose series). Dextran (I) showed an additional peak at *ca.* 794 cm.$^{-1}$ (α-1 : 3-linkages) (cf. Barker, Bourne, Stacey, and Whiffen [16]).

Both dextran (I) and dextran (II) were subjected to periodate oxidation. The procedure

[14] Bayly and Bourne, *ibid.*, 1953, **171**, 385.
[15] Foster, *Chem. and Ind.*, 1952, 828.
[16] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.

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adopted was essentially that of Jeanes and Wilham [17] which incorporates Fleury and Lange's method [18] for the determination of the quantity of periodate consumed, and that of Halsall, Hirst, and Jones,[19] with certain modifications, for the determination of the quantity of formic acid produced. The number of mols. of sodium periodate consumed per mol. of anhydroglucose was: 48 hr., 1·80 (I), 1·85 (II); 72 hr., 1·85 (I), 1·97 (II); 96 hr., 1·86 (I), 2·02 (II). The corresponding figures for mols. of formic acid produced were: 48 hr., 0·69 (I), 0·88 (II); 72 hr., 0·84 (I), 0·90 (II); 96 hr., 0·84 (I), 0·90 (II).

The solutions remaining from the oxidations of the dextrans were treated with excess of ethylene glycol, concentrated *in vacuo*, made 2N with sulphuric acid, and hydrolysed for 4 hr. at 100°. After neutralisation with barium carbonate each hydrolysate was concentrated *in vacuo* to 2 c.c. and submitted to chromatographic analysis. Visual comparison with suitable standards showed that periodate-oxidised dextran (I) gave *ca.* 10% of glucose and periodate-oxidised dextran (II) less than 5% of glucose after acid-hydrolysis.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15. [*Received, April 4th*, 1957.]

[17] Jeanes and Wilham, *J. Amer. Chem. Soc.*, 1950, **72**, 2655.
[18] Fleury and Lange, *J. Pharm. Chim.*, 1933, **17**, 107, 196.
[19] Halsall, Hirst, and Jones, *J.*, 1947, 1427.

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700. *Immunopolysaccharides. Part VII.*[1] *The Transglucosylase Action of* Betacoccus arabinosaceous *Dextransucrase.*

By R. W. BAILEY, S. A. BARKER, E. J. BOURNE, and M. STACEY.

Dextransucrase isolated from maltose–sucrose cultures of *B. arabinosaceous* contained only small amounts of dextran and the slight activity it exhibited with sucrose alone was increased almost fivefold by the addition of maltose. The isolation and characterisation of various oligosaccharides from sucrose–maltose and sucrose–methyl α-D-glucoside cultures is described.

IT was envisaged (Bailey, Barker, Bourne, and Stacey [1]) that growth of *Betacoccus arabinosaceous* on a medium containing maltose as well as sucrose would provide a source much depleted of dextran and might render possible the isolation of dextran-free dextransucrase. Although dextransucrase isolated under these conditions could not be completely freed from dextran, such preparations contained only one-tenth of the dextran present in the dextransucrase isolated from cultures containing sucrose alone.[1] The enzyme was isolated by fractionation with ethanol and dialysed to remove contaminating oligosaccharides and residual alcohol since the latter, if retained, would render the enzyme inactive (Table 2).

This dextransucrase exhibited several marked differences in properties from the heavily dextran-complexed dextransucrase.[1] It was much more unstable to heat; more than half its activity was lost after 3 days at 25° (Table 3). Its optimum temperature and pH, *ca.* 25° and 5·0 respectively, differed little however from those of dextransucrase isolated from sucrose cultures.

The major difference was that a dextransucrase with low dextran content exhibited only slight activity when incubated with sucrose alone. The addition of maltose, however, increased the rate of fructose production by values of up to 300—400%. In the presence of other sugars, particularly isomaltose, methyl α-D-glucoside, and D-glucose, the rates of fructose production were proportionately higher than those with a dextransucrase of high dextran content.[1] The inhibition of the reaction by fructose was similarly enhanced (Table 7). The synthesis of additional oligosaccharides was observed when the added sugar was maltose, isomaltose, methyl α-D-glucoside, D-glucose, cellobiose, or lactose.

[1] Part VI, Bailey, Barker, Bourne, and Stacey, preceding paper.

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These oligosaccharides were more readily available by actual growth of the organism in the presence of these added sugars. Fractionation of a maltose–sucrose culture after growth for 48 hr. at 25° gave crystalline panose having the correct physical constants, and the homologous tetra- and penta-saccharides produced by the transfer of one and two glucose units respectively in α-1 : 6-linkage to the non-reducing end of panose. These structures of the tetra- and penta-saccharide were suggested by examination of the products of complete and partial hydrolysis. Periodate oxidation of the alcohols of the tetra- and penta-saccharide confirmed these assignments. The tetrasaccharide alcohol consumed 9·02 mols. of periodate and produced 3·83 mols. of formic acid and 1·91 mols. of formaldehyde per mol. of alcohol. The theoretical figures are 9, 4, and 2 respectively. The penta-saccharide alcohol consumed 11·2 mols. of periodate and produced 4·75 mols. of formic acid and 1·85 mols. of formaldehyde per mol. of alcohol. The theoretical figures are 11, 5, and 2 respectively.

Fractionation of a methyl α-D-glucoside–sucrose culture after growth at 25° for 5 days gave chromatographically pure fractions of a suspected methyl α-bioside and a methyl α-trioside. Both were non-reducing, showed the correct methoxyl contents, and on complete hydrolysis gave glucose as the only sugar. Paper-chromatographic examination of their partial hydrolysates showed isomaltose among the products from the methyl α-bioside, and isomaltotriose among those from the methyl α-trioside. This suggested that the compounds were methyl α-isomaltoside and methyl α-isomaltotrioside, respectively. These structures were confirmed by periodate oxidation. The methyl α-bioside consumed 3·94 mols. of periodate and produced 2·1 mols. of formic acid per mol. of glycoside. The theoretical figures are 4 and 2 respectively. The methyl α-trioside consumed 5·96 mols. of periodate and produced 2·64 mols. of formic acid per mol. of glycoside. The theoretical figures are 6 and 3 respectively. Similar glycosides have been recently isolated [2] by the action of *Leuconostoc mesenteroides* dextransucrase on sucrose–methyl α-glucoside mixtures.

The synthesis of such oligosaccharides confirmed the view that the principal, but probably not the only (cf. ref. 1), function of the dextransucrase was the transfer of glucose residues in α-1 : 6-linkage to the non-reducing end-group of the sugar acceptor. This view was also supported by the detection of isomaltose, isomaltotriose, etc., in a sucrose–glucose culture.

Experimental

Standard Method of Isolation of Dextransucrase with Low Dextran Content.—An aqueous medium (140 c.c.) containing yeast extract (1%), $Na_2NH_4PO_4$ (0·5%), KH_2PO_4 (0·1%), $MgSO_4$, $7H_2O$ (0·05%), sucrose (2%), and maltose (10%) was adjusted with sodium hydroxide to pH 7·0, steam-sterilised at 15 lb./sq. in. for 30 min., and readjusted to pH 7·0 under sterile conditions. After inoculation with *Betacoccus arabinosaceous* (Birmingham strain), it was incubated at 25° for 30—36 hr. until the pH of the culture was 5·90.

The bacterial cells were removed by centrifuging and ethanol (47 c.c.; final concentration 25% v/v) was added to the culture fluid while the temperature was kept at 0° in this and subsequent operations. After 1 hr., the suspension was centrifuged and the precipitate, which contained 6% of the dextransucrase originally present in the culture, when estimated by the standard method in the presence of 100 mg. of maltose, was discarded. A further precipitate, containing 25% of the original dextransucrase activity, was likewise discarded after centrifuging the suspension obtained by addition of further ethanol (13 c.c.; final concentration 30% v/v).

The supernatant liquid was cooled to −20° and more ethanol (80 c.c.; final concentration 50% v/v) was slowly added with stirring. The suspension was kept at −20° for 1 hr. and then centrifuged at −18° for 20 min. (2000 r.p.m.). The heavy precipitate was dissolved in 0·05M-citrate buffer (pH 5·0; 40 c.c.) and dialysed for 48 hr. against 0·05M-citrate buffer (pH 5·0; 2 × 2 l.) at 0° in dialysis tubing that had been thoroughly washed with distilled water and 0·05M-citrate buffer (pH 5·0). The solution was then freeze-dried to a powder (0·702 g.) which showed only slight dextransucrase activity in the absence of a primer molecule but which, in

[2] Jones, Jeanes, Stringer, and Tsuchiya, *J. Amer. Chem. Soc.*, 1956, **78**, 2499.

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the presence of maltose (100 mg.), exhibited a 373% increase in the rate of fructose production from sucrose and then displayed 19% of the original dextransucrase activity in the culture fluid.

Standard Method for the Determination of Dextransucrase Activity.—The standard method described [1] for the estimation of dextransucrase with high dextran content was also used for the assay of preparations isolated from sucrose–maltose cultures except that, owing to the low activity of the latter enzyme in the absence of a primer molecule, an additional digest was incubated containing maltose (100 mg.), enzyme (2 c.c.), and sucrose (300 mg.) in 0·05M-acetate buffer (pH 5·0; 3 c.c.). In determinations of the activity of the centrifuged culture fluid (no maltose added) the amount of fructose it contained already was allowed for in calculating the dextransucrase activity.

Development of the Standard Method of Isolation of Dextransucrase with Low Dextran Content.—Preliminary experiments showed a high yield of oligosaccharides (see below) and very little dextran when the bacterium was cultured in a medium containing 50% of maltose and 10% of sucrose. Excessive wastage of maltose was avoided by using 10% of maltose and 2% of sucrose in the standard medium.

(a) *Time of growth.* A standard medium was inoculated and incubated at 25°. Aliquot parts were withdrawn at intervals for the measurement of pH and dextransucrase content of the centrifuged culture fluid (Table 1). The culture did not become viscous.

TABLE 1. *Effect of time of growth.*

Time (hr.)	0	16	23	38	48
pH of culture	7·0	6·6	6·45	5·05	4·2
Dextransucrase activity (units/c.c.)	—	0·9	1·5	5·5	4·7

(b) *Fractionation with ethanol.* Culture fluid (90 c.c.) containing 6 units/c.c. was cooled to 0° and ethanol (48 c.c.; final concentration 35% v/v) was added slowly with stirring. After 1 hr. at 0° the suspension was centrifuged at 0° and the precipitate dissolved in 0·05M-citrate buffer (pH 5·0; 50 c.c.), to give fraction A. The alcoholic supernatant solution was cooled to −20° and ethanol (42 c.c.) added slowly with stirring. After 30 min. at −20° the suspension was centrifuged at −18° and the brown precipitate obtained dissolved in 0·05M-citrate buffer (pH 5·0; 50 c.c.), to give fraction B. A portion of this solution was dialysed at 0° for 24 hr. against 0·05M-citrate buffer (pH 5·0; 2 × 2 l.), to give fraction C. After freeze-drying of part of this solution, the brown powder obtained was redissolved to give fraction D. The activities are in Table 2.

TABLE 2. *Activity of enzyme fractions.*

Fraction	A	B	C	D
Dextransucrase recovered (%)	37	0	12·5	12·5
Maltose priming power (%)	+100	0	+400	+400

Stability of Dextransucrase.—Purified enzyme (75 mg.) prepared by the standard method was dissolved in 0·02M-acetate buffer (pH 5·0; 12 c.c.) and stored in a tightly stoppered flask immersed in a thermostat at 25°. At intervals, the activity of aliquot portions (2 c.c.) was determined by the standard method in the presence of maltose (100 mg.) after incubation for 20 hr. (see Table 3).

TABLE 3. *Stability of dextransucrase.*

Time (hr.)	0	24	48	72	96
Activity (units/2 c.c.)	4·5	3·18	2·62	2·12	1·81

Carbohydrate Content of Dextransucrase.—A solution of enzyme (20 mg./c.c.) was submitted to paper partition chromatography with the organic phase of a mixture of butanol (40%), ethanol (10%), water (49%), and ammonia (1%). Spraying with alkaline silver nitrate [3] disclosed no sugars. Part (1 c.c.) of the enzyme solution was hydrolysed by 2N-sulphuric acid at 100° for 4 hr. After neutralisation with barium carbonate, filtration, and chromatography, a faint spot corresponding to glucose could be detected when 0·1 ml. of the filtrate was applied. Quantitative estimates (Shaffer and Hartmann [4]) of the glucose produced after hydrolysis of two batches of enzyme prepared by the standard method were 7·26% and 7·84% respectively.

Stability of Fructose in the Presence of the Enzyme.—Fructose (10 mg.) in 0·05M-acetate

[3] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[4] Shaffer and Hartmann, *J. Biol. Chem.*, 1921, **45**, 377.

buffer (pH 5·0; 2 c.c.) was incubated with enzyme (1 c.c.) for 20 hr. at 25°. Reducing power corresponding to 10·02 mg. of fructose could then be detected.

Effect of pH *on Enzyme Activity.*—Portions of freeze-dried dextransucrase with low dextran content were dissolved in water and the solutions adjusted to pH 4, 5, and 6 severally. Aliquot parts (2 c.c.) of each solution containing 20 mg. of enzyme, were mixed with sucrose (300 mg.) and maltose (100 mg.) dissolved in 0·05M-acetate buffer (10 c.c.) of the same pH, and the enzyme activity was measured after 20 hours' incubation at 25° (see Table 4).

TABLE 4. *Effect of* pH *on enzyme activity.*

pH	4·0	5·0	6·0
Apparent activity (units/20 mg. of enzyme)	0·0	6·75	3·36

Effect of Temperature on Enzyme Activity.—The activity of portions (20 mg.) of the enzyme was measured by the standard method after incubation at various temperatures for 20 hr. in the presence of sucrose (300 mg.) and maltose (100 mg.) dissolved in 0·05M-acetate buffer (pH 5·0; 7 c.c.) (see Table 5).

TABLE 5. *Effect of temperature on enzyme activity.*

Temp.	19°	25°	29°	36°
Apparent activity (units/20 mg. of enzyme)	4·62	6·75	4·62	0·90

Effect of Added Maltose on Enzyme Activity.—The activity of portions (20 mg.) of freeze-dried enzyme was measured by the standard method after incubation for 20 hr. at 25° in the presence of various amounts of maltose (see Table 6).

TABLE 6. *Effect of added maltose on enzyme activity.*

Maltose (mg.)	0	12·5	25	50	75	100	200
Fructose produced (mg.)	15·5	31·0	37·2	52·5	57·0	67·5	72·5
Increase in fructose production (%)	—	100	140	238	268	335	368

Effect of Added Sugars on Enzyme Activity.—The activity of dextransucrase (20 mg. portions) was measured by the standard method in the presence of a series of sugars (100 mg. each) which were added to the digests as their solutions in 0·05M-acetate buffer (2 c.c.; pH 5·0). Control digests to determine the effect of the enzyme on the added sugar alone were also prepared and incubated (20 hr.). Suitable aliquot portions were submitted to alkaline oxidation, and the fructose was estimated in the usual way (see Table 7).

TABLE 7. *Effect of added sugars on enzyme activity.*

Added sugar	Change in fructose yield (%)	Added sugar	Change in fructose yield (%)
Isomaltose	+351	Melibiose	+20·0
Maltose	+335	αα-Trehalose	+12·9
Methyl α-D-glucoside	+100	D-Galactose	+ 2·8
D-Glucose	+ 32	α-D-Glucose 1-phosphate	0·0
Cellobiose	+ 18·8	Fructose	−36·0
Lactose	+ 15·9		

Chromatographic examination of the digests revealed the presence of additional oligosaccharides where the added sugars were maltose, isomaltose, methyl α-D-glucoside, D-glucose cellobiose, and lactose, severally.

Oligosaccharide Synthesis by Growing Cultures of Betacoccus arabinosaceous *in the Presence of Added Sugars.*—(a) *Maltose–sucrose medium.* The same medium (40 c.c.) that was used for the production of low dextran content dextransucrase was inoculated with *Betacoccus arabinosaceous*, and incubated for 48 hr. at 25°. The culture (pH 4·26) was adjusted to pH 7·0 (with N-sodium hydroxide), additional sucrose (4 g.) added, and the culture incubated for a further 48 hr. The culture was neutralised, centrifuged, and heated for 10 min. at 90°, and the mixture separated on a charcoal–Celite column (l. 40 cm.; diam. 4 cm.) by elution with aqueous ethanol (Whistler and Durso [5]). Fructose (3·0 g.) [containing some glucose and an unknown ketose-containing disaccharide ($R_{glucose}$ 0·56)] and maltose (3·6 g.) were eluted with water (1·5 l.) and 5% aqueous ethanol (2 l.), respectively. Pure trisaccharide I (1·24 g.) and a mixed fraction

[5] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.

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(2·07 g.), containing trisaccharide I together with small amounts of maltose and tetrasaccharide II, were eluted with 5% aqueous ethanol (5 l.) and 10% aqueous ethanol (1 l.). Crude tetrasaccharide II (1·25 g.) and pentasaccharide III (0·92 g.) were removed with 10% aqueous ethanol (2 l.) and 15% aqueous ethanol (3 l.), respectively. A higher oligosaccharide fraction (1·65 g.) was obtained with 30% aqueous ethanol (1 l.). Refractionation of the crude tetra- and penta-saccharide fractions on a charcoal column gave tetrasaccharide II (0·4 g.) and pentasaccharide III (0·29 g.), both chromatographically pure.

(b) *Characterisation of the oligosaccharides.* Trisaccharide I, after two crystallisations from methanol–water (4 : 1 v/v), had m. p. 222—224°, undepressed on admixture with panose. It showed $[\alpha]_D^{21}$ +155·9° ⟶ +153·9° (18 hr.) (*c* 0·974 in H_2O) (Found: C, 42·9; H, 6·2. Calc. for $C_{18}H_{32}O_{16}$: C, 42·9; H, 6·4%). Its infrared spectrum in the region 1027—715 cm.$^{-1}$ and mobility as a benzylamine complex [7] on a paper chromatogram irrigated with butanol–ethanol–water–ammonia (40 : 12 : 20 : 1) were identical with those of panose.

Tetrasaccharide II moved as a single component $R_{glucose}$ 0·16 (cf. panose, $R_{glucose}$ 0·29) when separated as a benzylamine complex.[7] Paper ionophoresis of the benzylamine complex in formic acid [8] confirmed that it was a tetraose (mobility 0·476). The sugar showed $[\alpha]_D^{19}$ +164·1° (*c* 1·06 in H_2O) and its reducing power (Shaffer–Hartmann method [4]) was equivalent to 24·6% of that of glucose (cf. theor., 27·0%). Complete hydrolysis of the tetrasaccharide (5·3 mg.) with 1·5N-sulphuric acid for 4 hr. at 100° gave glucose (identified on a paper chromatogram) equivalent to a 94·2% conversion. Paper chromatographic analysis of a partial hydrolysate (N-sulphuric acid for 1 hr. at 90°) of the tetrasaccharide showed components with R_F values identical with those of glucose, isomaltose, maltose, panose, isomaltotriose, and tetrasaccharide II. A portion of the tetrasaccharide (0·1 g.) was reduced with an aqueous solution of sodium borohydride (0·1 g. in 50 c.c.) at room temperature for 2 hr. The tetrasaccharide alcohol was recovered as a freeze-dried powder {0·077 g.; $[\alpha]_D^{19}$ +120° (*c* 0·86 in H_2O)} after use of Amberlite IR-120 to remove sodium ions and distillation with methanol to remove boric acid. Treatment of the alcohol of the tetrasaccharide (41·4 mg.) in water (50 c.c.) with 0·25M-sodium periodate (5 c.c.) in the dark at room temperature gave the following results: The periodate consumption, expressed in mol. per mol. of alcohol, was: 3·85 (0·25 hr), 6·92 (1 hr.), 7·73 (2 hr.), 9·02 (4 hr.), 9·02 (6 hr.). After 6 hr., 3·83 mols. of formic acid and 1·91 mols. of formaldehyde were produced per mol. of alcohol.

Pentasaccharide III had $R_{Glucose}$ 0·10 when separated as benzylamine complex and showed $[\alpha]_D^{19}$ +167° (*c* 0·736 in H_2O), and a reducing value equivalent to 13·5% that of glucose (theor., 21·7%). Complete hydrolysis of the pentasaccharide (as above) gave glucose (identified on a paper chromatogram) equivalent to a 95·5% conversion. Paper chromatography of a partial hydrolysate (prepared as for the tetrasaccharide) of the pentasaccharide showed components with R_F values identical with those of glucose, isomaltose, maltose, panose, isomaltotriose, tetrasaccharides, and the original pentasaccharide. Reduction of the pentasaccharide (77 mg.) with sodium borohydride (as above) gave the corresponding alcohol (48 mg.), $[\alpha]_D^{19}$ +150° (*c* 0·96 in H_2O). On periodate oxidation (as above), the mols. of periodate consumed per mol. of alcohol were: 3·5 (0·25 hr.), 6·0 (1 hr.), 10·25 (3 hr.), 10·83 (5 hr.), 11·20 (6 hr.), 11·20 (10 hr.). After 10 hr., 4·75 mols. of formic acid and 1·85 mols. of formaldehyde were produced per mol. of alcohol.

(c) *Methyl* α-D-*glucoside–sucrose medium.* Standard medium (50 c.c.), in which the maltose was replaced by methyl α-D-glucoside (12·5 g.), was inoculated with *Betacoccus arabinosaceous* and incubated at 25° for 5 days. The culture was neutralised with N-sodium hydroxide, then heated at 90° for 10 min., and the mixture separated on a charcoal–Celite column (l. 30 cm.; diam. 3 cm.). Elution with water (3·5 l.) removed glucose, fructose, and some methyl α-D-glucoside. The remainder of the methyl α-D-glucoside was removed with aqueous ethanol (1%; 2 l.), and the suspected methyl α-bioside IV (0·884 g.) with 3% aqueous ethanol (1 l.) and 4% aqueous ethanol (2 l.). A mixed fraction (0·1 g.) containing suspected methyl α-bioside and methyl α-trioside was eluted with 6% aqueous ethanol (1 l.). Chromatographically pure methyl α-trioside V (0·506 g.) was obtained on washing with 10% aqueous ethanol (2 l.) and 12·5% aqueous ethanol (1 l.).

(d) *Characterisation of oligosaccharides* IV *and* V. The methyl α-bioside was non-reducing

[6] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[7] Bayly and Bourne, *Nature*, 1953, **171**, 385.
[8] Barker, Bourne, Grant, and Stacey, *ibid.*, 1956, **177**, 1125.

to Shaffer–Hartmann reagent,[4] had an $R_{Glucose}$ value of 0·68 (cf. isomaltose, 0·37) in the organic phase of a mixture of butanol–ethanol–water–ammonia (40 : 10 : 49 : 1), and showed $[\alpha]_D^{19}$ +169° (*c* 0·848 in H_2O) (Found: OMe, 8·4. Calc. for $C_{13}H_{24}O_{11}$: OMe, 8·7%). Complete hydrolysis of the methyl α-bioside (6·44 mg.) with 1·5N-sulphuric acid for 4 hr. at 100° gave glucose as the only sugar (identified paper-chromatographically) equivalent to a 95·7% conversion. Paper chromatography of a partial hydrolysate (N-sulphuric acid for 1 hr. at 90°) of IV showed components with R_F values identical with those of methyl α-D-glucoside, glucose, methyl α-bioside, and isomaltose. Oxidation of IV (52·6 mg.) in aqueous solution (50 c.c.) with 0·25M-sodium periodate (10 c.c.) consumed, as mols. of periodate per mol. of IV: 3·42 (2 hr.), 3·75 (10 hr.), 3·94 (24 hr.). After 24 hr., 2·1 mols. of formic acid were produced per mol. of IV.

The methyl α-trioside V was non-reducing to Shaffer–Hartmann reagent,[4] had an $R_{Glucose}$ value of 0·24 in the organic phase of a mixture of butanol–ethanol–water–ammonia (40 : 10 : 49 : 1), and showed $[\alpha]_D^{19}$ +176·3° (*c* 1·12 in H_2O) (Found: OMe, 6·2. Calc. for $C_{19}H_{34}O_{16}$: OMe, 6·0%). Complete hydrolysis of V (8·89 mg.) with 1·5N-sulphuric acid for 4 hr. at 100° gave glucose as the only sugar (identified paper-chromatographically) equivalent to a 98·1% conversion. Paper chromatography of a partial hydrolysate (N-sulphuric acid for 1 hr. at 90°) of V showed components with R_F values identical with those of methyl α-D-glucoside, glucose, methyl α-bioside, isomaltose, isomaltotriose, and methyl α-trioside. Oxidation of V (44 mg.) with sodium periodate (as with IV) consumed as mols. of periodate per mol. of V: 3·05 (0·25 hr.), 4·67 (2 hr.), 5·18 (4 hr.), 5·73 (6 hr.), 5·80 (8 hr.) and 5·96 (23 hr.). After 23 hr. 2·64 mols. of formic acid were produced per mol. of V.

(e) *Other sugar–sucrose media.* Standard media, in which the maltose was replaced by D-glucose (10%, 20%) or D-galactose (25%, 30%), were inoculated with *Betacoccus arabinosaceous* and incubated at 25°. Analysis of aliquot parts removed during incubation showed (i) the production of isomaltose, isomaltotriose, and higher oligosaccharides in the presence of added glucose and (ii) di- and tri-saccharide production in the presence of added galactose. No new oligosaccharides could be detected in cultures containing added melibiose (10, 20, or 40%) or raffinose (40%) incubated under the same conditions.

One of us (R. W. B.) thanks the Colonial Products Research Council for the award of a scholarship.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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701. *Studies of* Aspergillus niger. *Part VII.* The Enzymic Synthesis of* 3-O-β-D-*Glucopyranosyl*-D-*xylose.*

By S. A. BARKER, E. J. BOURNE, G. C. HEWITT, and M. STACEY.

A disaccharide produced by the action of a cell-free extract of *A. niger* (152) on a cellobiose–xylose mixture has been characterised as 3-*O*-β-D-glucopyranosyl-D-xylose.

WE have reported [1] that when a cell-free extract of *A. niger* (152) is incubated with a cellobiose–D-xylose mixture two unknown components (X, Y), with the mobilities of disaccharides, are produced in addition to those formed on incubation of the cell-free extract and cellobiose alone. We now report the isolation and characterisation of one of these components, disaccharide X.

After fractionation on a charcoal column [2] and thereafter on a Grycksbo filter-paper column, chromatographically pure X was isolated from the oligosaccharide mixture. The other unidentified component Y was produced only in minute amount. When separated by ionophoresis as its *N*-benzylglycosylammonium ion, X had the mobility expected [3] of a glucosylxylose. On the assumption that oxidation with hypoiodite was quantitative,[4] the

* Part VI, *J.*, 1957, 2448.

[1] Barker, Bourne, Hewitt, and Stacey, *J.*, 1955, 3734.
[2] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[3] Barker, Bourne, Grant, and Stacey, *Nature*, 1956, **177**, 1125.
[4] Hirst, Hough, and Jones, *J.*, 1949, 928.

XUM

molecular weight of disaccharide X was 281 (a glucosylxylose requires 312). The elementary analysis of X was in good agreement with a molecular formula $C_{11}H_{20}O_{10},H_2O$—the presence of water was confirmed by infrared analysis.

Acid hydrolysis of disaccharide X gave only glucose and xylose. The sequence of sugar units was determined by reduction of X to its alcohol and subsequent acid hydrolysis. Only glucose and xylitol could be detected in the hydrolysate, indicating that X was a glucosylxylose. The low optical rotation ($[\alpha]_D$ −0·6°) and the infrared spectrum [5] of X both indicated that the glycosidic linkage was β. The fact that both X and its osazone were attacked by emulsin was further confirmation of this structural feature.

Since X formed a disaccharide osazone (rather than being broken down into a mixture of monosaccharide osazones) the glycosidic linkage was not 1 : 2. Disaccharide X reacted rapidly with methanolic hydrogen chloride at room temperature. This indicated methyl furanoside formation and hence that the 4-hydroxyl group of the reducing sugar unit was free. The methyl furanoside of disaccharide X was isolated and methylated with sodium hydroxide–methyl sulphate and thereafter with the Purdie reagents. The methoxyl content (53·2%) was in good agreement with the value of 52·9% expected for a hepta-*O*-methyl derivative of a glucosylxylose. Hydrolysis of the methyl ether gave 2 : 3 : 4 : 6-tetra-*O*-methylglucose and a di-*O*-methylxylose. The latter (which could be differentiated chromatographically from both 3 : 4- and 2 : 4-di-*O*-methylxylose) was reduced to the corresponding xylitol derivative. When oxidised with sodium periodate the di-*O*-methylxylitol consumed almost 1 mol. of periodate and produced no formaldehyde or formic acid. The only di-*O*-methylxylitol (other than 1 : 4) which would give these values on oxidation is the 2 : 5-di-*O*-methyl derivative. This would only have been produced if the original disaccharide X was 3-*O*-β-D-glucopyranosyl-D-xylose, a structure which is consistent with the observation that X, when subjected to filter-paper ionophoresis in borate buffer, pH 10, had the same mobility as laminaribiose and gentiobiose, and moved much faster than cellobiose and sophorose.

The alcohol of disaccharide X appears to be overoxidised with periodate. Although the alcohol would be expected to consume 4 mols. of periodate and liberate 1 mol. of formic acid and 2 mols. of formaldehyde, a rapid uptake of 3 mols. of periodate followed by a slow uptake of another 4 mols. of periodate, making 7 mols. in all, was observed. After this time, 3·6 mols. of formic acid and 3·5 mols. of formaldehyde were liberated. This over-oxidation may be due to the formation of a substituted malondialdehyde structure, which would be expected with a 1 : 3-linked glucosylxylitol, but the phenomenon is very sensitive to reaction conditions and no attempt has been made to employ these results in the determination of the structure of disaccharide X.

Experimental

Enzymic Synthesis of Disaccharide X.—Cellobiose (15 g.) and D-xylose (15 g.) were dissolved in a cell-free extract [1] (50 c.c.) of *Aspergillus niger* (152) (*ca.* 9 g.) and incubated at 30° for 48 hr. The pH of the solution was then adjusted to 7 with sodium hydroxide and enzyme action arrested by boiling for 20 min. Paper-chromatography in the organic phase of butanol–ethanol–water–ammonia (40 : 10 : 49 : 1) revealed the presence of components having R_P values identical with those of xylose, glucose, laminaribiose, and cellobiose together with two unknown disaccharides X and Y (trace). After fractionation on a charcoal column [2] [gradient elution with aqueous ethanol (0 ⟶ 20%)], the monosaccharide fraction and a fraction containing cellobiose and a trace of gentiobiose were discarded. Attempts to fractionate the disaccharide mixture of X, Y, cellobiose, and laminaribiose on a cellulose and on a charcoal column in the presence of borate [6] were unsuccessful. Fractionation was finally achieved on a 3391 Grycksbo chromatographic filter-paper column with the organic phase of a butanol (40), ethanol (10), and water (50) mixture. Those fractions containing disaccharide X only were combined, concentrated, and dried to a white powder (1·40 g.), $[\alpha]_D^{19}$ −0·6° (*c* 0·35 in H_2O).

[5] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[6] Barker, Bourne, and Theander, *J.*, 1955, 4276.

Characterisation of Disaccharide X.—(i) The *compound* (Found: C, 40·0; H, 6·9. $C_{11}H_{20}O_{10}$ requires C, 42·2; H, 6·45. $C_{11}H_{20}O_{10}.H_2O$ requires C, 40·0; H, 6·7%), had infrared absorption at 1640 ± 5 cm.$^{-1}$ due to water. In the range 700—1100 cm.$^{-1}$ absorption peaks were at 1021, 936, 895, 758, and 719 cm.$^{-1}$.

(ii) *Paper chromatography and ionophoresis.* Paper chromatography of the free sugar and of its benzylamine derivative [7] in the first solvent mixture described above showed that disaccharide X was chromatographically pure and moved with an R_P between those of laminaribiose and glucose. When submitted to paper ionophoresis [8] in borate buffer, pH 10, the mobility of disaccharide X was approx. the same as those of laminaribiose and gentiobiose. When separated as its *N*-benzylglycosylammonium ion in an electrolyte of sodium hydroxide–formic acid (pH 1·8),[3] the mobility (M) was 0·80.

(iii) *Oxidation with hypoiodite.* A series of solutions containing glucose, xylose, and disaccharide X was oxidised with iodine in alkaline solution (Hirst, Hough, and Jones [4]). Glucose and xylose were oxidised stoicheiometrically. The molecular weight of disaccharide X, calculated on the assumption that the oxidation was stoicheiometric, was 281.

(iv) *Formation of osazone.* Disaccharide X (25 mg. in 0·4 c.c.), with phenylhydrazine (50 mg.) and 50% acetic acid (0·05 c.c.) at 100° for 2 hr., gave yellow crystals after cooling which after recrystallisation from ethanol had m. p. 213—215°. On circular paper chromatography in toluene–ethanol–water (270 : 30 : 1), the osazone had an R_P approx. the same as that of cellobiosazone and very different from those of glucosazone and xylosazone.

The osazone (5 mg.), dissolved in dioxan (0·2 c.c.), was treated with almond emulsion (5 mg.). Paper chromatography showed that the only free sugar liberated was glucose. Electrophoresis [3] in sodium formate–formic acid (pH 1·8) showed that while the mobility of the disaccharide X osazone was approx. the same as that of cellobiosazone, the product of almond emulsin action had the mobility of a monosaccharide osazone.

(v) *Hydrolysis.* Disaccharide X (2 mg.) was heated with 1·5N-sulphuric acid at 100° for 2 hr. The solution was neutralised with barium carbonate and filtered. Disaccharide X (10 mg.) was incubated with almond emulsin (10 mg. in 0·2 c.c. of water) at 30° for 2 days. Paper chromatography of both the acidic and the enzymic hydrolysate showed only the presence of glucose and xylose.

(vi) *Reduction.* Disaccharide X (25 mg.) in water (12 c.c.) was reduced with sodium borohydride (25 mg.) at room temperature for 2 hr. Amberlite IR-120 (H^+) (1 g.) was added and the mixture shaken for 15 min., then filtered and evaporated to dryness *in vacuo*. Dry methanol (3 × 15 c.c.) was added and the whole evaporated to dryness *in vacuo*. The residue was dissolved in water and freeze-dried.

Part of the disaccharide alcohol (2 mg.) was heated with 2N-sulphuric acid at 100° for 2 hr. Paper chromatography of the neutral hydrolysate and selective spraying with aniline hydrogen phthalate and buffered bromocresol-purple revealed the presence of components having R_P values identical with those of glucose and xylitol. The same sprays indicated that the disaccharide alcohol moved as a single component.

The disaccharide alcohol (15·8 mg.) was oxidised with 0·025M-sodium periodate (50 c.c.) at 18°. Some mannitol (11·2 mg.) was similarly treated. Results were:

Mols. of periodate consumed per:						
mol. of disaccharide alcohol	2·9	6·0	—	6·5	6·8
mol. of mannitol	4·8	—	5·0	5·0	5·0
Time (hr.)	0·5	23·25	27	47·5	124

After 124 hr., 3·6 mols. of formic acid and 3·6 mols. of formaldehyde were produced per mol. of disaccharide alcohol.

(vii) *Conversion into its methyl furanoside.* Disaccharide X (900 mg.) was left in 4% methanolic hydrogen chloride (40 c.c.) at room temperature for 1·5 hr. before being neutralised with silver carbonate (8 g.). After filtration, the solution was concentrated *in vacuo* and then freeze-dried to a white powder (692 mg.) (Found: OMe, 10·1. Methyl glucosylxyloside requires OMe, 9·5%).

(viii) *Methylation of the methyl furanoside.* The methyl furanoside (686 mg.) was suspended in dioxan (20 c.c.) and methylated with dimethyl sulphate (35 c.c.) and 30% aqueous sodium hydroxide (70 c.c.), added in ten equal portions at 10 min. intervals. The product (618 mg.) was then methylated three times with the Purdie reagent. The resulting syrup (462 mg.)

[7] Bayly and Bourne, *Nature*, 1953, **171**, 385.
[8] Foster, *J.*, 1953, 982.

XUM

(Found: OMe, 52·2. Hepta-*O*-methylglucosylxylose requires OMe, 52·9%) showed neglible infrared absorption in the O–H stretching region (3400—3700 cm.$^{-1}$).

(viii) *Hydrolysis of methylated disaccharide X.* The methyl ether (440 mg.) was heated with 0·5N-sulphuric acid (15 c.c.) at 100° for 2 hr., and the solution neutralised with barium carbonate, filtered, and evaporated to a syrup (305 mg.). Paper chromatography of the syrup showed that it contained only two components, one with an R_F identical with that of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and the other with an R_F somewhat less than those of 3 : 4- and 2 : 4-di-*O*-methylxylose.

The syrup was fractionated by Bell's method [9] to give 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose (171 mg.) and the new di-*O*-methylxylose {63 mg.; $[\alpha]_D^{19}$ +11·5° (*c* 0·31 in $CHCl_3$)}. The latter was reduced to the alcohol with sodium borohydride (50 mg.) as described for disaccharide X. On periodate oxidation the di-*O*-methylpentitol consumed 0·5 (0·25 hr.), 0·9 (3 hr.), and 0·9 mol. (25 hr.) of periodate. No formic acid or formaldehyde was produced.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15. [*Received, April 12th,* 1957.]

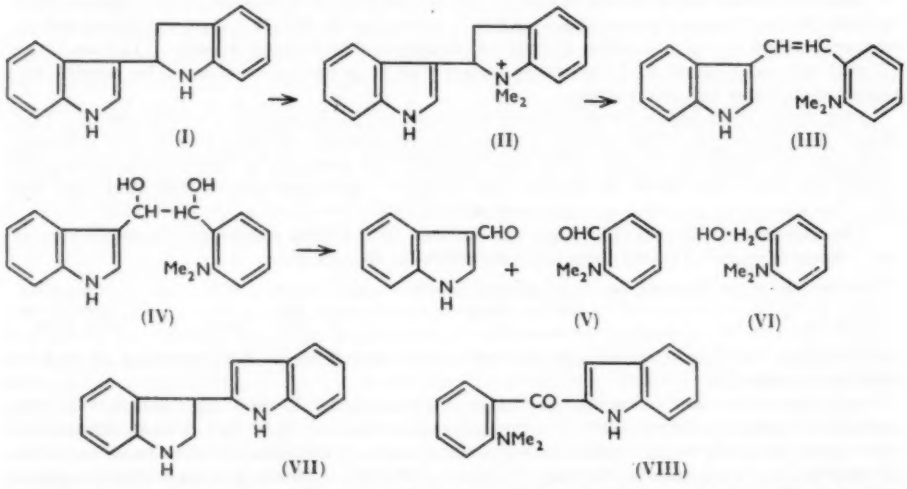
[9] Bell, *J.*, 1944, 473.

702. *Indoles. Part II.* The Structure of Indole Dimer.*

By H. F. HODSON and G. F. SMITH.

Structure (I) for indole dimer [1] is substantiated by a degradation.

IN a previous communication,[1] structure (I) was proposed for indole dimer, on the basis of mechanistic arguments. We have now confirmed it by a degradation. The dimer was converted by methyl iodide and anhydrous potassium carbonate in acetone into the methyl methiodide (as II), which underwent normal Hofmann degradation to the methine



(III). With osmium tetroxide this yielded the crystalline diol (IV), which with periodate gave 3-formylindole in 82% yield and a liquid base, presumably *o*-dimethylaminobenzaldehyde (V); the base was reduced by sodium borohydride to 2-dimethylaminobenzyl alcohol (VI), characterised as the picrate. Authentic 2-dimethylaminobenzyl alcohol

* Part I, Smith, *J.*, 1954, 3842.

[1] Smith, *Chem. and Ind.*, 1954, 1451.

was prepared by reduction of methyl *NN*-dimethylanthranilate with lithium aluminium hydride.

The structure (VII) proposed by Schmitz-DuMont *et al.*[2] for indole dimer would have required the above degradation to lead to formaldehyde and the ketone (VIII).

Experimental

M. p.s are corrected.

2-3′-*Indolyl*-1 : 1-*dimethylindolinium iodide* (as II). Indole dimer (3 g.) in dry acetone (100 c.c.) was refluxed for 6 hr. with methyl iodide (10 g.) and potassium carbonate (10 g.). After evaporation under reduced pressure, the residue was washed with ether, then very thoroughly with cold water. Crystallisation from methanol yielded the *iodide* as prisms, m. p. 195—197° (3·8 g., 86%) (Found: C, 55·05; H, 4·9; N, 6·6. $C_{18}H_{19}N_2I$ requires C, 55·4; H, 4·9; N, 7·15%).

3-2′-*Dimethylaminostyrylindole picrate* (cf. III). The iodide (2·83 g.) was refluxed for 15 min. in 15% aqueous-ethanolic sodium hydroxide (100 c.c.), most of the ethanol removed under reduced pressure, and the residue treated with water (30 c.c.) and extracted with ether (3 × 30 c.c.). The combined, dried (K_2CO_3) extracts gave a pale brown liquid (1·92 g.), which from methanol solution gave a *picrate* (3·57 g., 82%), orange prisms, m. p. 145—149° (from acetone) (Found: C, 58·4; H, 4·25; N, 14·0. $C_{18}H_{18}N_2,C_6H_3O_7N_3$ requires C, 58·65; H, 4·3; N, 14·25%). The base, liberated from the picrate, did not crystallise.

2′-*Dimethylaminophenyl*-1-3′-*indolylethane*-1 : 2-*diol* (IV). The methine (62·5 mg.) in dry ether (2 c.c.) containing 3 drops of pyridine was treated at 0° with osmium tetroxide (100 mg.) in dry ether (10 c.c.). After being kept overnight at room temperature, the brown osmate–pyridine complex was filtered off, washed with ether, dissolved in methylene chloride (15 c.c.), and shaken with 10% aqueous mannitol (20 c.c.) containing 1% of potassium hydroxide. The methylene chloride solution was separated and the aqueous layer extracted further with methylene chloride (5 × 10 c.c.). The combined dried extracts yielded the *diol* (58·7 mg.) which crystallised from methanol as prisms, m. p. 183—185° (50·0 mg., 70·5%) (Found: C, 72·5; H, 6·9; N, 9·6. $C_{18}H_{20}O_2N_2$ requires C, 72·9; H, 6·8; N, 9·5%).

Periodate fission. The diol (80 mg.) in aqueous ethanol was treated at 0° with sodium metaperiodate (70 mg.) in water (1 c.c.). After 2 hr. at 0°, the ethanol was boiled off under reduced pressure, and the residue diluted with water (5 c.c.) and extracted with ether (4 × 10 c.c.). The combined extracts were divided into basic and non-basic fractions. The non-basic fraction (41 mg.) crystallised, to give a pinkish solid, m. p. 188—193°. Sublimation, followed by crystallisation from aqueous methanol, gave 3-formylindole as colourless plates, m. p. and mixed m. p. 194—196° (32 mg., 82%). The basic fraction (18·5 mg.) was treated in methanol (3 c.c.) with sodium borohydride (35 mg.) and kept at 40° for 2 hr. The methanol was boiled off under reduced pressure, water (10 c.c.) was added, and the whole was extracted with ether (3 × 10 c.c.). The combined, dried extracts yielded a colourless liquid (16·0 mg.) which with picric acid (24 mg.) in benzene yielded a picrate, m. p. 120—127°. One crystallisation from methanol gave yellow elongated prisms, m. p. 128—130°, undepressed on admixture with 2-dimethylaminobenzyl alcohol picrate. The free base, recovered from the picrate and distilled at 80° (oil-bath)/0·01 mm., had an infrared spectrum (liquid film) identical with that of authentic 2-dimethylaminobenzyl alcohol.

2-*Dimethylaminobenzyl alcohol* (VI).—Methyl *NN*-dimethylanthranilate[3] (10 g.) in dry ether (100 c.c.) was treated dropwise with an excess of ethereal lithium aluminium hydride. After 4 hr. at room temperature, the mixture was slowly treated with water (15 c.c.), 40% aqueous sodium hydroxide (30 c.c.) was added, the whole shaken, and the ether layer separated. This yielded **2-*dimethylaminobenzyl alcohol*** (7·7 g., 96%), b. p. 115°/8 mm. (Found: C, 71·6; H, 8·6; N, 9·7. $C_9H_{13}ON$ requires C, 71·5; H, 8·65; N, 9·3%). The *picrate* forms yellow prisms (from ethanol), m. p. 129—130° (Found: C, 47·5; H, 4·65; N, 14·6. $C_9H_{13}ON,C_6H_3O_7N_3$ requires C, 47·35; H, 4·25; N, 14·75%).

We are indebted to the University College of North Staffordshire for a Tutorial Studentship (to H. F. H.).

University College of North Staffordshire.
The University, Manchester. [*Received, April 12th*, 1957.]

[2] Schmitz-DuMont, Hamann, and Geller, *Annalen*, 1933, **504**, 1.
[3] Willstätter and Kahn, *Ber.*, 1904, **37**, 408.

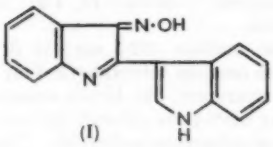
XUM

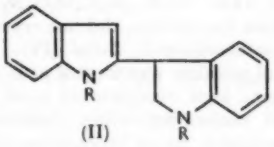
703. *Indoles. Part III.* The Structure of Zatti and Ferratini's "Dinitrosoindole."*

By H. F. Hodson and G. F. Smith.

Structure (IV) is proposed for "dinitrosoindole," mainly on the basis of ultraviolet spectra.

Nitrosation of indole in aqueous acetic acid, first studied systematically by Zatti and Ferratini in 1890,[1] proceeds in a complex manner to yield a very dark tar from which two compounds can be isolated: one is indole red, shown by Seidel [2] in 1944 to have structure (I), and the other is an almost colourless compound shown [3] to be $C_{16}H_{12}O_2N_4$ and called "dinitrosoindole." It is different from the deep yellow dinitrosoindole dimer prepared by Schmitz-DuMont *et al.*[4] by the nitrosation of indole dimer and formulated by them as (II; R = NO). Seidel [2] found that "dinitrosoindole" decomposes in pyridine solution to indole red (I): this indicated the presence in "dinitrosoindole" of an αβ-di-indolyl skeleton,


(I)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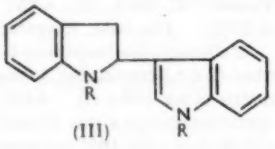
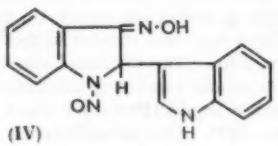

(III)

and led Seidel to propose the alternative structure (III; R = NO) for the compound. Indole dimer having been shown to have structure (III; R = H) (see preceding paper), the structure of its dinitroso-derivative must be (III; R = NO), that already given to "dinitrosoindole" by Seidel. This reopens the question of the structure of Zatti and Ferratini's "dinitrosoindole."

That "dinitrosoindole" cannot have structure (II; R = NO) is immediately shown by the strong and complex absorption this compound shows in the NH and OH stretching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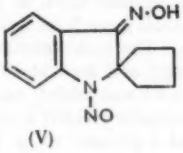
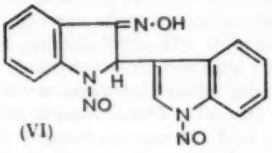
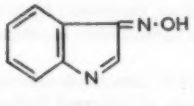

(V)


(VI)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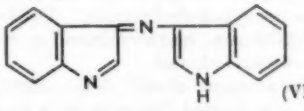

(VIII)

region of the infrared spectrum. It is profitable also to consider ultraviolet spectra: both compounds (II; R = NO) and (III; R = NO) contain unconjugated *N*-nitrosoindole and *N*-nitrosoindoline chromophores, and one would expect their ultraviolet spectra to be very similar.† The ultraviolet spectra of dinitrosoindole dimer and of "dinitrosoindole" are in fact markedly different (Fig. 1, curve *a*; Fig. 2, curve *a*). It was at this

* Part II, preceding paper.

† One of the Referees has drawn our attention to the fact that hyperconjugation through a saturated carbon atom (CH_2) has been found to affect ultraviolet absorption (Braude, *J.*, 1949, 1902). The effect is, however, only a minor one and for our purposes negligible.

[1] Zatti and Ferratini, *Ber.*, 1890, **23**, 2299.
[2] Seidel, *Ber.*, 1944—1946, **77—79**, 797.
[3] Zatti and Ferratini, *Gazzetta*, 1892, **21**, 19.
[4] Schmitz-DuMont, Hamann, and Geller, *Annalen*, 1933, **504**, 1.

stage found that a sum of the ultraviolet spectra of *N*-nitrososkatole and of 1-nitroso-2-methylindoline is very similar indeed to the spectrum of dinitrosoindole dimer (Fig. 1). From this it is clear that the deep yellow colour of dinitrosoindole dimer is due to the *N*-nitrosoindole system present in it.

That " dinitrosoindole " is colourless suggests that it does not contain an *N*-nitrosoindole system : this, and the formation of indole red (I) from it under mild conditions,[2] can be accounted for satisfactorily only by structure (IV). This view is supported by the

FIG. 1.

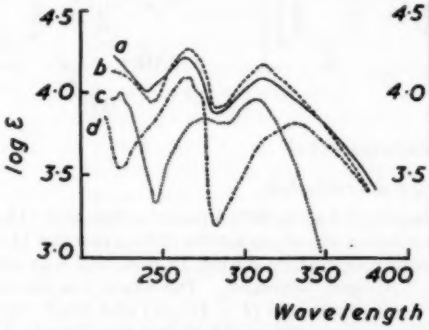


FIG. 2.

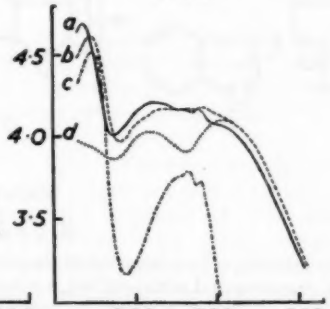


FIG. 1. *a, Dinitrosoindole dimer* (III; R = NO) *in* n-*hexane*; *b, sum of c and d*; *c,* 2-*methyl*-1-*nitrosoindoline in* n-*hexane*; *d,* N-*nitrososkatole in* n-*hexane.*

FIG. 2. *a,* " *Dinitrosoindole* " (IV); *b, sum of c and d*; *c, skatole*; *d,* cyclo*pentane*spiro-2-(3-*hydroxyimino*-1-*nitrosoindoline*) (V). *All in* EtOH.

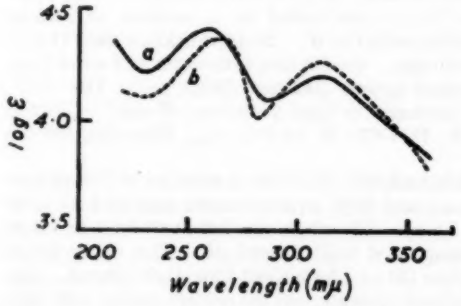


FIG. 3. *a, Nitroso-derivative of " dinitrosoindole "* (VI) *in* EtOH; *b, sum of* cyclo*pentane*spiro-2-(3-*hydroxyimino*-1-*nitrosoindoline*) (V) *in* EtOH *and* N-*nitrososkatole in* n-*hexane.*

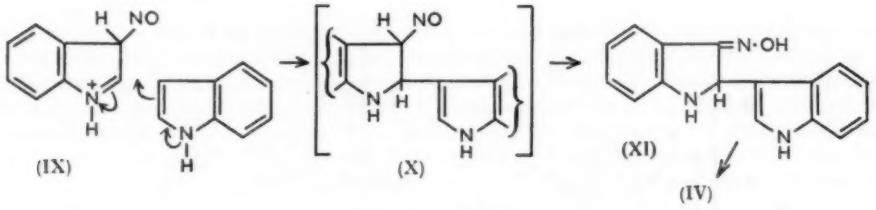
fact that the sum of the ultraviolet spectra of cyclopentane*spiro*-2-(3-hydroxyimino-1-nitrosoindoline) (V) and skatole corresponds very closely to the spectrum of " dinitrosoindole " (Fig. 2). Further, we have found that " dinitrosoindole " forms a yellow nitroso-derivative which must have structure (VI) : in accord with this its ultraviolet spectrum is closely similar to the sum of the spectra of (V) and *N*-nitrososkatole (Fig. 3).

To test the idea that " dinitrosoindole " (IV) is formed by acid-catalysed condensation of initially formed hydroxyiminoindolenine (VII) with indole, we studied the interaction of these two compounds in aqueous acetic acid. The only isolable product was a deep blue crystalline compound, $C_{18}H_{15}O_2N_3$, which is probably the acetate of di-3-indolylazamethine (VIII) : such a condensation of a hydroxyimino-group with a reactive position is well known in the formation of indophenols; a closer analogy is found in the formation of dipyrrylazamethines by condensation of nitrosopyrroles with pyrroles in acetic acid.[5]

[5] Rogers, *J.*, 1943, 590.

It is evident, therefore, that " dinitrosoindole " (IV) is not formed by way of (VII); it is therefore likely that it is the immediate product of addition of a nitrosonium ion to indole (IX), which gives (X), which then rearranges to (XI), and is further nitrosated to " dinitrosoindole " (IV).

N-Nitrososkatole had previously been inadequately characterised:[6] we have now obtained it as a homogeneous product, m. p. 10—12°, which gives correct analyses.



Experimental

M. p.s are corrected.

N-*Nitrososkatole*.—To a solution of skatole (1·3 g.) in 90% aqueous acetic acid (12 c.c.) at 0° was added, dropwise and with swirling, a solution of sodium nitrite (2·0 g.) in water (4 c.c.) at 0°. The mixture was allowed to warm to room temperature during 15 min. and was poured into excess of cold saturated aqueous sodium hydrogen carbonate. The whole was extracted with *n*-pentane, the extracts were washed with 95% methanol (2 × 10 c.c.) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was pure N-*nitrososkatole*, a yellow, very unstable, viscous liquid crystallising at 0° to a solid, m. p. 10—12° (Found: C, 67·5; H, 4·6. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%), $\lambda_{max.}$ 264, 329—334 mμ (ε 12,560, 6515) in *n*-hexane.

cyclo*Pentane*spiro-2-(3-*hydroxyimino*-1-*nitrosoindoline*) (V).—*cyclo*Pentane*spiro*-2-(3-hydroxyiminoindoline)[7] (350 mg.) in methanol (5 c.c.) was added to a solution of sodium nitrite (160 mg.) in water (1 c.c.) and the solution cooled to 0°. 2N-Hydrochloric acid (1 c.c.) was added dropwise and the whole left at 0° for 30 min. On dilution with water and scratching, the *nitroso-compound* separated as very pale yellow prisms (312 mg., 78%), m. p. 110—113°, unchanged by recrystallisation from aqueous methanol or light petroleum (Found: C, 62·5; H, 5·5; N, 17·9. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·67; N, 18·2%), $\lambda_{max.}$ 259—262, 305 mμ (ε 10,800, 12,600) in EtOH.

3-*Hydroxyimino*-1-*nitroso*-2-(1-*nitroso*-3-*indolyl*)*indoline* (VI).—To a solution of " dinitrosoindole " (500 mg.) in dimethylformamide (6 c.c.) and 95% aqueous acetic acid (6 c.c.) at 0° was added sodium nitrite (350 mg.) in water (1 c.c.). The whole was left at 0° for 1 hr., then poured into ice-water (100 c.c.), and the precipitated solid filtered off. This ochre-yellow powder (480 mg.) was digested with warm benzene (30 c.c.) for a short time, then filtered. The benzene was boiled off from the filtrate under reduced pressure, and the reddish residue (260 mg.) dissolved in ethanol (4 c.c.) at 50°: on cooling to 0°, the solution deposited the *nitroso-compound* (173 mg.) as a yellow crystalline powder, decomp. 130—132°, unchanged by further crystallisation (Found: C, 59·9; H, 3·8; N, 21·3. $C_{16}H_{11}O_3N_5$ requires C, 59·8; H, 3·5; N, 21·8%).

The work was carried out during the tenure of a grant from the Schunck Fund of the University of Manchester (to H. F. H).

The University, Manchester. [*Received, April 12th*, 1957.]

[6] Fischer, *Annalen*, 1886, **236**, 140.
[7] Beer, McGrath, and Robertson, *J.*, 1950, 2126.

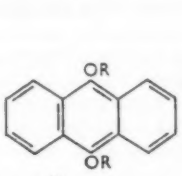
704. *Sulphuric Esters of Polycyclic Quinols.*

By William Bradley and John Gerald Lee.

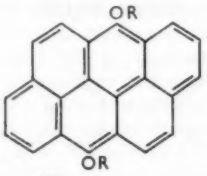
Salts of the disulphuric esters of quinol, anthraquinol, 6 : 12-dihydroxyanthanthrene, and 3 : 8-dihydroxy-1 : 2-6 : 7-dibenzopyrene have been prepared and studied. None undergoes replacement of the groups $-O\cdot SO_3^-$ with the nucleophilic agents studied, but all are readily hydrolysed by acids and oxidised to the related quinones with acid oxidants.

Although many of the sulphuric esters of quinols have become important technically, because of the ease with which they are oxidised to the parent quinones,[1] little has been published about their general chemistry. Their preparation generally involves acylation of a quinol [2] or reduction of a quinone in the presence of an acylating agent,[3,4,5] and both methods have been used in the present work.

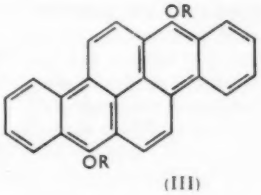
The sulphuric esters are known to be unstable in light [6] or in acid solution, and most are readily soluble in water and difficult to purify. The present investigation was concerned mainly with the sodium and potassium salts of the di-*O*-sulphuric esters of anthraquinol (I), 6 : 12-dihydroxyanthanthrene (II), and 3 : 8-dihydroxy-1 : 2-6 : 7-dibenzopyrene (III). These were prepared by reduction of the corresponding quinones with iron powder in pyridine in the presence of chlorosulphonic acid, essentially by the method already described,[3] and were best purified by crystallisation from water, which generally gave hydrates. The corresponding barium salts were more sparingly soluble in water and unstable. The disodium salt of the di-*O*-sulphuric ester of *leuco*indigotin has been obtained both as decahydrate [1] and tetrahydrate.[7]



(I)



(II)



(III)

The sodium salts were reduced to the corresponding aromatic hydrocarbon in 10—20% yield on being shaken in alcohol suspension with Raney nickel.[8] Each gave the quinone on oxidation with aqueous ferric chloride or nitrous acid. When chlorine- or bromine-water, acidified hydrogen peroxide (with or without ferrous sulphate), or potassium persulphate was used the product contained a small proportion of phenolic compounds. With the anthracene derivative (I) the principal phenolic product had almost the same absorption spectrum in concentrated sulphuric acid as 2-hydroxyanthraquinone; a smaller proportion of 1-hydroxyanthraquinone was formed also. The anthanthrene derivative (II) gave a phenolic product which differed from the known 3 : 9-dihydroxyanthranthrone [9] and was not an *o*-hydroxycarbonyl compound. The salts did not show any simple reaction with such nucleophilic reagents as aniline, potassium cyanide, potassium ethoxide, or

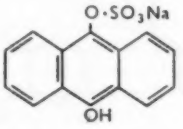
[1] Bader, *Chimie et Industrie*, 1924, Nos. 449, 445.
[2] Baumann, *Ber.*, 1878, **11**, 1907; Verley, *Bull. Soc. chim. France*, 1901, **25**, 46; Scalera, Hardy, Hardy, and Joyce, *J. Amer. Chem. Soc.*, 1951, **73**, 3094; U.S.P. 403,226.
[3] Jones, Wylam, Morton, and Morton Sundour Fabrics, B.P. 245,587, 248,802, 251,491.
[4] Coffey, *Chem. and Ind.*, 1953, 1068; B.P. 633,408.
[5] G.P. 489,725, 520,031.
[6] Gerhard and Dierkes, *Rayonne et Fibres*, 1953, **9**, No. 4, 43; B.P. 734,932.
[7] Ruggli and Stauble, *Helv. Chim. Acta*, 1940, **23**, 689.
[8] Cf. Jain, Mittel, and Seshadri, *J. Sci. Ind. Res., India*, 1953, **12**, *B*, No. 12, 647.
[9] Bradley and Waller, *J.*, 1953, 3778.

XUM

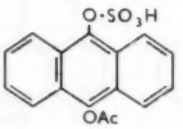
potassium benzoate. In this they resembled sodium phenyl sulphate [10] rather than sodium methyl sulphate, although the first reacts with sodium phenoxide in liquid ammonia to form diphenyl ether,[11] and potassium phenyl sulphate affords phenyl benzoate with potassium benzoate.[12] The potassium salt of (I) showed no tendency to react with bromine or ferric chloride in benzene. All the salts were notably stable towards hot aqueous alkalis but were decomposed on the addition of acid to their aqueous solutions.[13] From boric acid and a suspension of the salt (I; R = SO_3Na) in aniline, heated rapidly to the boiling point, 9 : 10-dianilinoanthracene was readily formed: Liebermann [14] obtained the same product similarly from 9 : 10-diacetoxyanthracene.

When anhydrous the salts were unexpectedly stable to heat in the absence of air, but decomposition occurred rapidly when both air and moisture were present. The salts were relatively stable towards alkaline oxidants but acid oxidants changed them into the related quinones at rates which greatly exceeded the rates of hydrolysis in the absence of oxidising agents. Bader [1] considered that in acid oxidation hydrolysis of both sulphate groups occurred, the quinol so formed being an essential intermediate. Later he held that oxidation occurred directly and that hydrolysis was not involved.[15] Another view of the reaction suggests that in the presence of hydrogen peroxide hydrolysis of one sulphate group occurs first, the resulting phenol being oxidised through a radical; [16] this accords better with the present results.

The importance of the monosulphates as intermediates in the acid oxidation of the disulphates of quinols is evident from two considerations. Rapid oxidation to the related quinone does not take place except in the presence of an effective (acid) hydrolytic agent. Neither free monosulphate nor free quinol can be detected in the presence of nitrous acid though in the absence of this the presence of the monosulphate can be demonstrated. 10-Hydroxy-9-anthryl hydrogen sulphate (as IV) which was used in these experiments was not isolated. It was prepared from oxanthrone acetate by reaction with triethylamine–



(IV)



(V)

sulphur trioxide and hydrolysis of the resulting salt of 10-acetoxy-9-anthryl hydrogen sulphate (V) in alkaline solution. Parallel experiments with corresponding derivatives of quinol showed that phenols were more easily oxidised than their disulphates when the oxidant was nitrous acid in dilute sulphuric acid. Neither the diacetate nor the disulphate of quinol was changed on brief contact at 60° while the monoacetate and monosulphate were both oxidised. Experiments with potassium phenyl sulphate showed that the rate of hydrolysis of this with hydrochloric acid was not affected by the addition of hydrogen peroxide. The rate was, however, dependent on the medium, increasing in the series, water < water–alcohol (15 : 85 v/v) < water–acetone (34 : 66 v/v) < acetone.

Experimental

Disodium 9 : 10-Anthrylene Disulphate (I; R = SO_2Na).—Pyridine (50 g.) and chlorosulphonic acid (10 g.) were mixed below 20°, then heated to 60°. Anthraquinone (6 g.) and iron powder (4 g.) were added and the reactants were vigorously shaken at 60—70° for 3 hr. The resulting suspension was added to water (300 c.c.) containing sodium carbonate (15 g.),

[10] Burkhardt, Ford, and Singleton, *J.*, 1936, 17.
[11] Kranzfelder and Sowa, *J. Amer. Chem. Soc.*, 1937, **59**, 149.
[12] Czapek, *Monatsh.*, 1914, **35**, 637.
[13] Burkhardt and Lapworth, *J.*, 1926, 684.
[14] Liebermann, *Annalen*, 1934, **513**, 157.
[15] Bader, *Amer. Dyestuff Reporter*, 1938, **27**, 455.
[16] Ainsworth and Johnson, *J. Soc. Dyers and Colourists*, 1955, **71**, 592.

pyridine was removed in steam under reduced pressure, and the residual suspension was heated to 80° and then filtered, the residue being washed with a small volume of hot water. On the addition of salt to the combined filtrates to give a 10% solution of sodium chloride, pale yellow plates separated; these were collected and dried in a vacuum-desiccator (yield 11 g.). The use of a coarser grade of electrolytic iron in this preparation gave a slower reaction, and the best yields were obtained when the steam-distillation was carried out on a succession of small portions to avoid decomposition of the disulphuric ester.

The crude disodium salt (30 g.) was purified by dissolution at 90° in water (150 c.c.) containing a few drops of aqueous sodium hydroxide (charcoal), giving pale yellow plates. Disodium 9 : 10-anthrylene disulphate is very soluble in water to a pale yellow solution with an intense blue fluorescence. On addition of nitric acid, or sodium nitrite and acetic acid, anthraquinone, m. p. and mixed m. p. 281°, was precipitated in an almost pure form. Samples of the disodium salt which had been kept for 24 hr. over calcium chloride in an evacuated desiccator consisted of a *tetrahydrate* [Found: Na, 9·2; SO_4, 39·8; anthraquinone, 42·3. $C_{14}H_8(O{\cdot}SO_3Na)_2,4H_2O$ requires Na, 9·5; SO_4, 39·5; anthraquinone, 42·8%].

On the addition of an excess of dilute sulphuric acid to an aqueous solution of the disodium salt the blue-violet fluorescence increased in intensity. After short heating of the acidified solution at 60° in the absence of air, addition of an excess of dilute sodium hydroxide caused development of a yellow colour and a brick-red fluorescence in ultraviolet light (sodium 10-hydroxy-9-anthryl sulphate).

Dipotassium 9 : 10-Anthrylene Disulphate (I; R = SO_3K).—Excess of barium acetate was added to a solution of the disodium salt (5 g.) in water (100 c.c.). The salt which separated was collected, washed with barium hydroxide solution, then added to a hot solution of sufficient potassium sulphate to ensure precipitation of barium. Barium sulphate was removed, potassium chloride was added to the filtrate, and the dipotassium salt which separated in plates on cooling was recrystallised twice from water containing a small amount of potassium hydroxide. After being dried over calcium chloride in a vacuum-desiccator the resulting salt was a *dihydrate* [Found: loss at 80° *in vacuo*, 7·4; anthraquinone formed on oxidation, 42·5. $C_{14}H_8(O{\cdot}SO_3K)_2,2H_2O$ requires H_2O, 7·7; anthraquinone, 41·1%].

Disodium Anthanthren-6 : 12-ylene Disulphate (II, R = SO_3Na).—Prepared from anthanthrone (18 g.), chlorosulphonic acid (20 g.), pyridine (100 g.), and iron powder (4 g.) as described for the anthracene analogue, except that the amount of sodium carbonate used was 45 g., the crude disodium salt separated as bronze plates (70%). Two further crystallisations from water rendered just alkaline and subsequent drying in air gave the disodium salt as a yellow-brown *tetrahydrate* [Found: loss at 70° *in vacuo*, 12·4; SO_4, 31·8; 31·8, 32·0; anthanthrone formed on oxidation, 52·2, 52·6, 52·4. $C_{22}H_{10}(O{\cdot}SO_3Na)_2,4H_2O$ requires H_2O, 12·3; SO_4, 32·8; anthanthrone, 52·4%].

Disodium 1 : 2-6 : 7-Dibenzopyren-3 : 8-ylene Disulphate.—The dibenzopyrenequinone employed in this preparation was prepared by the action of benzoyl chloride on *meso*benzanthrone. When the quinone (18 g.) was treated with pyridine (108 g.), chlorosulphonic acid (22 g.), and iron powder (8 g.) at 60° for 4 hr., and the product was isolated as for the anthracene analogue, small orange crystals of disodium 1 : 2-6 : 7-dibenzopyren-3 : 8-ylene disulphate separated. Recrystallisation from water made just alkaline with sodium hydroxide gave the salt as an orange *dihydrate* [Found, in hydrated salt: H_2O, 5·48. $C_{24}H_{12}(O{\cdot}SO_3Na)_2,2H_2O$ requires H_2O, 6·25%], and this, on being heated in a vacuum drier at 100°, gave the yellow, anhydrous salt which deliquesced in air. The yellow aqueous solution showed a blue-green fluorescence ($\lambda_{max.}$ 390 and 480 mμ).

9-Toluene-p-sulphonyloxyanthracene.—Toluene-*p*-sulphonyl chloride (1·5 g.) was heated on a water-bath with a solution of anthrone (1·0 g.) in pyridine (2·5 c.c.); after 2 min. solidification occurred and was soon complete. Water (25 c.c.) was added, the whole was shaken, and the solid which separated was collected, and washed with dilute sodium hydroxide solution, and finally with water. Purification from alcohol gave the colourless *derivative*, m. p. 167—168° (Found: C, 72·7; H, 4·4; S, 9·05. $C_{21}H_{16}O_3S$ requires C, 72·4; H, 4·6; S, 9·2%).

Reduction Experiments.—(1) A solution of 9-toluene-*p*-sulphonyloxyanthracene (0·4 g.) in absolute alcohol (200 c.c.) was shaken overnight with a suspension (4 c.c. of settled suspension prepared by Vogel's method) of Raney nickel in alcohol. The resulting solid was collected and washed with benzene, and the benzene and alcohol solutions were combined and shaken with water (1 l.). The benzene layer which was formed was separated, washed, evaporated to

small volume, mixed with light petroleum (b. p. 60—80°; 150 c.c.), and chromatographed on alumina. Elution with light petroleum removed coloured material, and further treatment with benzene–light petroleum gave anthracene as colourless, blue-fluorescent plates, m. p. and mixed m. p. 209—212°.

(2) Dipotassium 9 : 10-anthrylene disulphate (0·5 g.), suspended in absolute alcohol (200 c.c.), was similarly reduced with Raney nickel (3 c.c. of alcoholic suspension); anthracene, m. p. 213° (0·036 g.), resulted. When the reactants were refluxed for 3 hr. instead of being shaken overnight the yield of anthracene was 0·041 g. Anthraquinone was also readily reduced in alcohol with Raney nickel but no anthracene could be isolated.

(3) Disodium anthanthren-6 : 12-ylene disulphate (0·5 g.) was shaken for 15 hr. with a suspension (3 c.c.) of Raney nickel in alcohol. The reactants exhibited an intense blue-green fluorescence and this was not changed during the reaction. The product was isolated substantially as with the anthracene derivative. The benzene-soluble part of the product was isolated and then chromatographed on alumina from light petroleum (b. p. 100—120°). The yellow band which formed was extracted with benzene affording yellow plates (0·04 g.). Refluxing the reactants for 3 hr. instead of shaking them gave the same product (0·08 g.). The products from the two preparations were combined and crystallised from benzene (20 c.c.); yellow plates of anthanthrene were obtained, having m. p. 261° alone or when mixed with the compound prepared by reduction of anthanthrone with hydriodic acid.[17] On being shaken with an alcohol suspension (3 c.c.) of Raney nickel in absolute alcohol (250 c.c.), anthanthrone (0·3 g.) gave 6 : 12-dihydroxyanthanthrene (violet coloration on the addition of sodium hydroxide solution) but no anthanthrene.

(4) Similar reduction of disodium 1 : 2-6 : 7-dibenzopyren-3 : 8-ylene disulphate (0·5 g.) by shaking overnight with Raney nickel in alcohol (3 c.c.) and isolation of the product as for the anthanthrene derivative gave yellow leaflets (0·02 g.) of 1 : 2-6 : 7-dibenzopyrene, m. p. 310°, alone or when mixed with the compound prepared by reduction of 1 : 2 : 6 : 7-dibenzopyrene-3 : 8-quinone with zinc dust, zinc chloride, and sodium chloride [18] (Found : C, 95·0; H, 4·65. Calc. for $C_{24}H_{14}$: C, 95·4; H, 4·6%).

Action of Heat on Salts of 9 : 10-*Anthrylene Dihydrogen Disulphate.*—(a) *Disodium salt.* On being heated rapidly to 90° in an acid-free atmosphere the tetrahydrate decomposed forming a green product; no sulphite ions could be detected. The green material dissolved in dilute sodium hydroxide with the deep red colour of anthraquinol. A solution containing 2 g. in warm 5% aqueous sodium hydroxide (100 c.c.) was aerated until the red colour disappeared. The resulting suspension was boiled, then filtered from anthraquinone, and the filtrate was acidified. The precipitate was crystallised from acetic acid, chromatographed on alumina, and treated with dilute sodium hydroxide solution. The following compounds were isolated : naphthadianthrone ($\lambda_{max.}$ in concentrated sulphuric acid, 512, 575; Brockmann [19] records 512, 537, 575 mμ); 10 : 10′-dianthronyl, m. p. 245°, giving a yellow green solution in concentrated sulphuric acid which was changed to red on being warmed; [20] dianthronol, m. p. 230°, giving a yellow fluorescent solution in benzene which became greener on being warmed, and a Bordeaux solution in concentrated sulphuric acid.[21]

Decomposition of the salt was greatly hastened by acid; even sodium hydrogen sulphate caused rapid decomposition at 65°. Heated in a vacuum the salt was much more stable.

(b) *Dipotassium salt.* The anhydrous salt was stable in air at 80°, and even at 100° decomposition was slight after 6 hr.; the product contained anthraquinone. Decomposition was still slow at 70° even after the salt had been mixed with potassium hydrogen sulphate. In a vacuum the salt changed little below 200°. At 200—220° decomposition was complete in 2 hr.; sulphur dioxide was present. In a further experiment the salt (1 g.) was heated to decomposition at 230—240° in a vacuum, the containing vessel was then cooled, and boiled-out aqueous potassium hydroxide (1 g. in 70 c.c.) was admitted. The resulting suspension was shaken and filtered, and the filtrate was added to 0·1N-iodine (50 c.c.). Back-titration with sodium thiosulphate solution showed that the product contained 0·066 g. of sulphur dioxide. Recrystallisation of the alkali-insoluble part (0·44 g.) gave anthraquinone. The alkali-insoluble

[17] Scholl and Meyer, *Ber.*, 1934, **67**, 1229.
[18] Clar, *Ber.*, 1939, **72**, 1645.
[19] Brockmann, *Annalen*, 1942, **553**, 1.
[20] Clar and Muller, *Ber.*, 1930, **63**, 869.
[21] Meyer, *Ber.*, 1909, **42**, 143.

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part (0·39 g.) obtained in a similar experiment gave anthraquinone, m. p. 281° (0·21 g.) and m. p. 277° (0·08 g.). The anhydrous potassium salt was stable to heat at 150° *in vacuo* with potassium hydrogen sulphate.

(c) *Salts of anthanthren-6 : 12-ylene dihydrogen disulphate.* The hydrated sodium salt was stable at 80° in air; above 90° decomposition occurred slowly. In the absence of air decomposition occurred at 150°, sulphur dioxide and 6 : 12-dihydroxyanthanthrene being formed. The anhydrous potassium salt was stable in air at 100°; above this temperature decomposition occurred. In the absence of air the salt was stable below 200°.

(d) *Disodium 1 : 2-6 : 7-dibenzopyren-3 : 8-ylene disulphate.* This was stable in air at 90° for 1·5 hr. In the absence of air the yellow anhydrous salt was formed first, then decomposed at ~160°, sulphur dioxide being liberated.

Action of Nucleophilic Agents on the Salts.—(1) *Aniline.* (*a*) With aniline (30 c.c.) at 100° for 3 hr. anhydrous dipotassium 9 : 10-anthrylene disulphate (1 g.) was unchanged. Refluxing for 15 min. decomposed the salt completely, forming anthraquinone in small amount and an unidentified red product; the same result was obtained after 3 hr. at 150°. No 9 : 10-dianilinoanthracene was formed in these experiments. When the salt (2 g.) was refluxed for 10 min. with aniline (10 c.c.) and boric acid (3 g.) a red solution resulted which contained 9 : 10-dianilinoanthracene. This was isolated by addition of the cooled product to 5% hydrochloric acid (150 c.c.), separation of the solid which formed, washing with methanol, extraction of a small proportion of anthraquinone with alkaline dithionite solution, and crystallisation of the insoluble part from xylene. The resulting yellow plates had m. p. 295—300°, alone or when mixed with 9 : 10-dianilinoanthracene prepared by Liebermann's method.[14]

(*b*) Dipotassium 1 : 2-6 : 7-dibenzopyren-3 : 8-ylene disulphate (4 g.) and aniline (15 c.c.) on being heated slowly to 150° and then kept for several hr. at this temperature gave 1 : 2-6 : 7-dibenzopyrene-3 : 8-quinone, but no nitrogen-containing derivative.

(2) *Potassium cyanide.* Dipotassium 9 : 10-anthrylene disulphate (1 g.) and potassium cyanide (1 g.) in water (40 c.c.) were heated at 125° for 3 hr. in a sealed tube. On being cooled the solution had a pale yellow colour and a few needles were present. Heating was continued at 140° for 6 hr. The cooled product contained much unchanged dipotassium salt; the needles which separated were anthraquinone. 9 : 10-Dicyanoanthracene [22] was absent.

(3) *Sodium ethoxide.* No reaction occurred when dipotassium 9 : 10-anthrylene disulphate (1 g.), sodium ethoxide (10 g.), and absolute alcohol (40 c.c.) were shaken together for 24 hr. When the same reactants were refluxed for 2 hr. a small amount of benzene-soluble material resulted but there was no indication of the presence of 9 : 10-diethoxyanthracene.[23]

Salts of 10-Acetoxy-9-anthryl Hydrogen Sulphate.—The triethylamine salt (Found : S, 7·1. Calc. for $C_{32}H_{37}O_6NS$: S, 7·4%) was prepared by Scalera, Hardy, Hardy, and Joyce's method.[2] A yellow colour developed (hydrolysis of acetyl group) on the addition of sodium hydroxide to its colourless solution in water. In this instability towards alkalis triethylammonium 10-acetoxy-9-anthryl sulphate differs from dipotassium 9 : 10-anthrylene disulphate. Solutions of both salts fluoresce blue in ultraviolet light, and that of the disulphate remains unaffected by the addition of sodium hydroxide whilst that of the 10-acetoxy-derivative changes to brick-red. Neither of the derivatives is immediately affected by the addition of an excess of dilute sulphuric acid and both readily yield anthraquinone on the further addition of sodium nitrite.

Potassium p-*Hydroxyphenyl Sulphate and Dipotassium* p-*Phenylene Disulphate.*—A solution of quinol (20 g.) in the minimum volume of pyridine was added to one of chlorosulphonic acid (21 g.) in pyridine (160 c.c.). The temperature was raised slowly to 65° and kept thereat for 3 hr., access of air being prevented. The resulting solution was added to water containing potassium hydroxide (45 g.), and pyridine was removed under reduced pressure. The filtered solution afforded large straw-coloured crystals on being cooled; recrystallisation from water gave the pure *dipotassium* p-*phenylene disulphate*, m. p. 287° (Found : C, 20·7; H, 1·1; S, 18·4; K, 22·8. $C_6H_4O_8S_2K_2$ requires C, 20·8; H, 1·2; S, 18·3; K, 23·2%). Salt was added to the mother-liquor to complete the precipitation and, after filtration, the mother-liquor was evaporated to dryness under reduced pressure and the residue extracted with hot 95% alcohol. On being cooled the extract gave brown crystals (14 g.), which gave colourless *potassium* p-*hydroxyphenyl sulphate* (6 g.), m. p. 220° (from alcohol) (Found : C, 31·4; H, 2·3; S, 14·0; K, 17·4. $C_6H_5O_5SK$ requires C, 31·6; H, 2·2; S, 14·0; K, 17·1%).

[22] Beyer and Fritsch, *Ber.*, 1941, **74**, 494.
[23] Meyer, *Annalen*, 1911, **379**, 37.

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Hydrolyses.—Effect of solvent on the rate of hydrolysis of sulphates. (1) Potassium phenyl sulphate (Found : C, 33·9; H, 2·7; S, 15·0; K, 18·2. Calc. for $C_6H_5O_4SK$: C, 33·9; H, 2·4; S, 15·0; K, 18·0%) was prepared by the action of chlorosulphonic acid on phenol in pyridine, the resulting phenyl hydrogen sulphate being converted into the potassium salt. 0·25N-Hydrochloric acid (10 c.c.) was added to an 0·1M-solution of potassium phenyl sulphate in (*a*) water (50 c.c.), (*b*) a mixture (50 c.c.) of water (1 vol.) and acetone (4 vols.) at 50° ± 0·2°. At intervals, volumes (10 c.c.) were withdrawn and titrated against 0·1N-sodium hydroxide (*p*-nitrophenol as indicator). Results were :

Time (hr.)		0	1	2	4	12	23
0·1N-NaOH required (c.c.)	(*a*)	4·0	4·1	4·2	4·45	5·2	6·4
	(*b*)	4·0	9·0	10·5	11·6	12·2 *	—

* Hydrolysis complete.

(2) 0·25N-Hydrochloric acid (10 c.c.) was heated at 50° ± 0·2° with (*a*) a 0·1M-solution (50 c.c.) of potassium *p*-hydroxyphenyl sulphate in water, (*b*) a 0·1M-solution (50 c.c.) of the same salt in acetone, and (*c*) a 0·05M-solution (50 c.c.) of dipotassium *p*-phenylene disulphate in water. Neutralisation (*p*-nitrophenol) of 10 c.c. of the solution required the stated volumes of alkali at the times recorded.

Time (hr.)		0	0·0833	1·0	2·0	3·0	6·0	19·0	22·0
0·1N-NaOH required (c.c.)	(*a*)	4·0	4·0	4·1	—	4·2	4·3	—	5·0
	(*b*)	4·0	4·2	—	10·7 *	—	—	—	—
	(*c*)	4·0	4·0	4·2	4·3	—	4·75	6·0	—

* $KHSO_4$ precipitated.

Oxidation of Disodium 9 : 10-Anthrylene Disulphate with Hydrogen Peroxide and Hydrochloric Acid. Formation of 2-Hydroxyanthraquinone.—Concentrated hydrochloric acid (10 c.c.) and 60-vol. hydrogen peroxide (40 c.c.) were added to a solution of the disodium salt (8 g.) in water (190 c.c.). After several hr. at 65° the reactants afforded a yellow precipitate (3·7 g.). (*a*) This was dissolved in toluene and the resulting solution was extracted with hot dilute aqueous sodium hydroxide containing 5% of alcohol. The bright red alkaline solution was boiled, treated with charcoal, and filtered. On being acidified the filtrate gave a bright yellow solid (0·23 g.) which had m. p. 305° after crystallisation from toluene. Its solution in concentrated sulphuric acid showed maximum absorption at 250, 290, 324, 414, and 490 mμ. (Meyer and Fischer [24] report maxima at 290, 320, 410, and 500 mμ for 2-hydroxyanthraquinone.) (*b*) In a second experiment the yellow precipitate was dissolved in toluene and chromatographed on alumina. Anthraquinone passed quickly through the column, leaving two bands which were separated and extracted with alcoholic hydrochloric acid. The extract was evaporated and the residue sublimed in a vertical tube; two bands were formed. The lower yellow band, the bulk of the adsorbed material, consisted of 2-hydroxyanthraquinone. The red upper band afforded 1-hydroxyanthraquinone, m. p. 186°, which gave a positive boroacetate test and a sparingly soluble, magenta barium salt. There was no indication of hydroxylation when finely divided anthraquinone was heated at 70° for 8 hr. with hydrochloric acid and hydrogen peroxide, or when disodium 9 : 10-anthrylene disulphate was heated with hydrogen peroxide in the absence of acid. Hydroxylation occurred, however, when the oxidant was hydrogen peroxide with acetic acid, or potassium persulphate with acetic acid, and rapidly when the oxidant was bromine-water, chlorine-water, or hydrogen peroxide–acetic acid–ferrous sulphate.

In parallel experiments with disodium anthanthren-6 : 12-ylene disulphate (4 g.) in water (100 c.c.), concentrated hydrochloric acid (5 c.c.) and 60-vol. hydrogen peroxide (20 c.c.) brick-red material separated from solution. A portion of this dissolved sparingly in dilute sodium hydroxide forming a blue solution, from which a small amount of a flocculent red precipitate was formed on acidification. The boroacetate test was negative.

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CLOTHWORKERS RESEARCH LABORATORY,
UNIVERSITY OF LEEDS.

[*Received, February 13th*, 1957.]

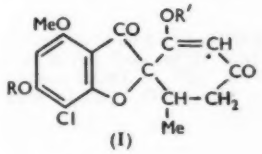
[24] Meyer and Fischer, *Ber.*, 1913, **46**, 90.

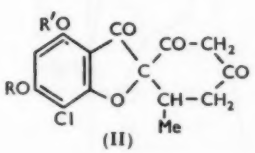
705. *Griseofulvin. Part XII.* Position of the Aryl Methyl Ether Linkage, Labile to Aqueous Alkali.*

By L. A. Duncanson, John Frederick Grove, J. MacMillan, and T. P. C. Mulholland.

Degradative and spectroscopic evidence is presented showing that it is the 6- and not the 4-methyl ether linkage in griseofulvin (and certain derivatives) which is hydrolysed by aqueous alkali. The stability to aqueous alkali of the methyl ether linkage in several model compounds, related to the aromatic ring in griseofulvin, has been investigated; ethers *para* to the carbonyl group in a 7-chlorocoumaranone are labile but those similarly situated in an acetophenone are stable. The methyl ethers of 4 : 6-dihydroxycoumaranone have been orientated unambiguously; the ultraviolet and infrared spectra of these compounds and of several derivatives of griseofulvin are discussed.

In griseofulvin (I; R = R′ = Me) and certain of its derivatives one of the aryl methyl ether linkages is hydrolysed by boiling aqueous alkali to give the corresponding phenol. Thus,[1,2] griseofulvin and 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (II; R = R′ = Me) with 0·5N-sodium hydroxide yield the phenol, 7-chloro-4(or 6)-hydroxy-6-(or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione (II; R = H or Me, R′ = Me or H).[3] Similarly [4] β-(7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-yl)butyric acid (III; R = R′ =


(I)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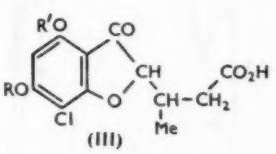
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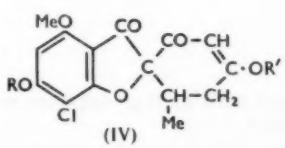
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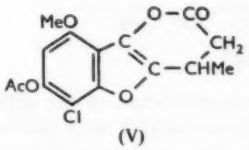
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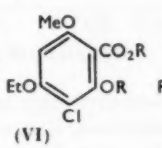
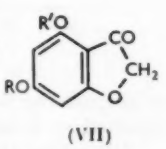

(VI)


(VII)

Me), an oxidation product of griseofulvin, yields with 3N-sodium hydroxide the phenolic acid (III; R = H or Me, R′ = Me or H), an oxidation product of the phenolic trione (II; R = H or Me, R′ = Me or H). Degradative and spectroscopic evidence is now presented showing that these phenols are 6-hydroxycoumaranones. The tentative suggestion in Part IV [3] that they were the 4-hydroxy-derivatives was first doubted when these phenols were found to give negative reactions with methanolic titanous chloride; the model 4-hydroxycoumaranones, described below, gave red colours with this reagent.

Degradative Evidence.—The phenolic trione (II; R = H, R′ = Me) with diazoethane yielded two isomeric diethyl ethers (I and IV; R = R′ = Et), distinguished by their ultraviolet light absorption.[2,3] The diethyl ether (I; R = R′ = Et) on permanganate oxidation gave 3-chloro-4-ethoxy-2-hydroxy-6-methoxybenzoic acid (VI; R = H) whose structure was established by methylation to an ester ether (VI; R = Me) identical with

* Part XI, *J.*, 1957, 3124.

[1] Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[3] *Idem*, *J.*, 1952, 3977.
[4] Grove, Ismay, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3958.

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an authentic specimen prepared by ethylation of methyl 3-chloro-4-hydroxy-2 : 6-dimethoxybenzoate.[5]

The phenolic trione derived from griseofulvin by aqueous alkaline hydrolysis is therefore (II; R = H, R′ = Me). It follows that the phenolic acid, derived from (III; R = R′ = Me), is (III; R = H, R′ = Me) and that the neutral lactonic acetate [4] formed therefrom is (V).

Ultraviolet and infrared spectra confirm the degradative conclusions. The model compounds were prepared by recorded methods except 4-hydroxy-6-methoxycoumaranone (VII; R = Me, R′ = H) which was prepared by the following adaption of Shriner and Witte's method [6] for 4-hydroxycoumaranone. 2 : 6-Dihydroxy-4-methoxyacetophenone [7] was converted *via* the diacetyl derivative into ω-bromo-2 : 6-dihydroxy-4-methoxyacetophenone which, on ring closure, afforded the coumaranone (VII; R = Me, R′ = H). This unambiguous synthesis finally establishes that the monomethyl ether, obtained by monomethylation of 4 : 6-dihydroxycoumaranone (VII; R = R′ = H) with diazomethane,[8] and also by ring closure of the Hoesch reaction product of chloroacetonitrile and phloroglucinol monomethyl ether,[8,9] is the 4-methyl ether (VII; R = H, R′ = Me). Attempts

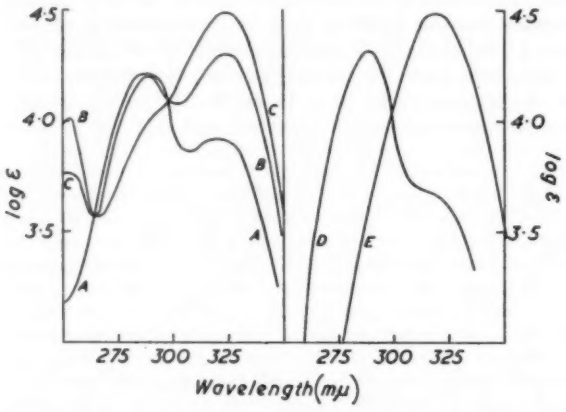


FIG. 1. *Ultraviolet absorption of the acid* (III; R = H, R′ = Me).

In EtOH, (*A*) 1·66 × 10⁻³M, (*B*) 2·16 × 10⁻⁴M, *and* (*C*) 2·16 × 10⁻⁵M. (*D*) *In* EtOH *containing* 2% *of* HCl. (*E*) *In* 0·1N-NaOH.

to prepare the 6-methyl ether by methylation of the diphenol with methyl sulphate as reported by Balakrishna, Rao, and Seshadri [10] were unsuccessful.

Ultraviolet Absorption Spectra.—Cram and Cranz [11] have shown that *o*- and *p*-hydroxyacetophenones can be distinguished by comparing their ultraviolet light absorption in ionising and non-ionising media. For *o*-hydroxy-derivatives, the *K*-band of both the anion and the undissociated molecule have maxima of similar intensity at about the same wavelength. In the *p*-hydroxy-series, the *K*-band of the anion occurs at a much longer wavelength and is more intense than that of the undissociated molecule. The model hydroxycoumaranones behaved in the same way (Table 1).

The 4-hydroxy-compound (VII; R = Me, R′ = H) absorbed at 280 mμ (*K*-band) as the undissociated molecule and at 285 mμ as the anion, a shift of only 5 mμ; with the 6-hydroxy-compound (VII; R = H, R′ = Me) there was a corresponding shift of 34 mμ. The phenolic acid (III; R = H, R′ = Me) showed absorption typical of a 6-hydroxycoumaranone. The spectrum of the phenolic trione (II; R = H, R′ = Me) is complicated

[5] Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967.
[6] Shriner and Witte, *J. Amer. Chem. Soc.*, 1939, **61**, 2328.
[7] Sönn and Bülow, *Ber.*, 1925, **58**, 1691.
[8] Geissman and Hinreiner, *J. Amer. Chem. Soc.*, 1951, **73**, 782.
[9] Gruber and Horvarth, *Monatsh.*, 1949, **80**, 563.
[10] Balakrishna, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, 1949, **29**, 394.
[11] Cram and Cranz, *J. Amer. Chem. Soc.*, 1950, **72**, 595.

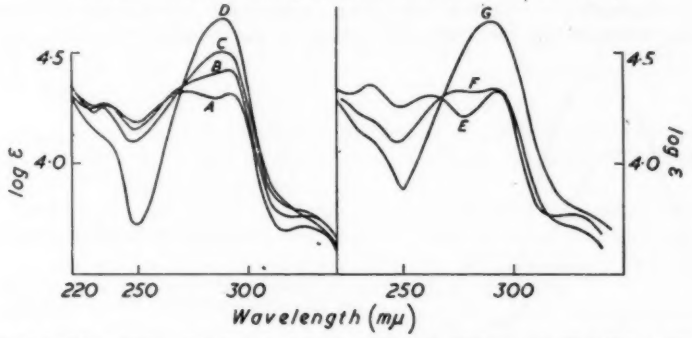
TABLE 1. *Ultraviolet-light absorption of hydroxycoumaranones* ($\lambda_{max.}$ *in* mμ).

	In ethanol + 2% HCl				In 0·1N-sodium hydroxide			
	K-band		*B*-band		*K*-band		*B*-band	
Compound	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
VII; R = Me, R′ = H	280	4·31	~315	3·63	285	4·35	346	3·81
VII; R = H, R′ = Me	284	4·35	~315	3·78	318	4·53		
VII; R = R′ = H	283	4·30	~312	3·83	306	4·51	~345	3·70
VII; R = R′ = Me	282	4·33	~318	3·72 *				
III; R = H, R′ = Me...	289	4·32	~320	3·68	320	4·52		
II; R = H, R′ = Me ...	292	4·30	~325	3·70 †	327	4·65		
II; R = R′ = Me	292	4·34	~330	3·70 †	291	4·65	~330	3·80

* In ethanol. † In ethanol–McIlvaine buffer pH 2·1 (1 : 1).

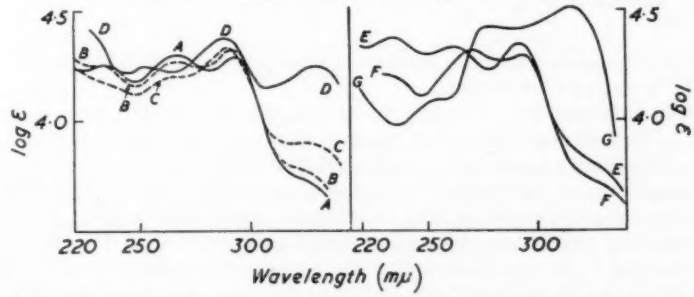
by the presence of the cyclic 1 : 3-dione chromophore (see Fig. 3 and below); however, the high-intensity band at 327 mμ in alkaline solution, absent from the spectrum of (II;

FIG. 2. *Ultraviolet absorption of the trione* (II; R = R′ = Me).



In EtOH, (*A*) 1·216 × 10⁻⁴M, (*B*) 6·08 × 10⁻⁵M, (*C*) 3·04 × 10⁻⁵M, *and* (*D*) 1·216 × 10⁻⁵M. (*E*) *In* EtOH *containing* 2% *of* HCl. (*F*) *In* 1 : 1-EtOH–*McIlvaine buffer* (pH 2·1), *and in* 0·5N-*ethanolic* HCl (pH 1·5). (*G*) *In* 0·1N-NaOH.

FIG. 3. *Ultraviolet absorption of the trione* (II; R = H, R′ = Me).



In EtOH, (*A*) 1·28 × 10⁻⁴M, (*B*) 1·28 × 10⁻⁵M, (*C*) 6·4 × 10⁻⁶M, *and* (*D*) 1·28 × 10⁻⁵M. (*E*) *In* EtOH *containing* 2% *of* HCl. (*F*) *In* 1 : 1 EtOH–*McIlvaine buffer* (pH 2·1). (*G*) *In* 0·1N-NaOH.

R = R′ = Me) in alkaline solution (Fig. 2), clearly demonstrates the presence of a 6-hydroxycoumaranone chromophore.

In ethanol, the absorption of the 6-hydroxy- but not the 4-hydroxy-coumaranones was dependent on concentration. The curves obtained at various concentrations lay between those of the anion and the undissociated molecule and showed a sharp isosbestic point. The curves (Fig. 1) for (III; R = H, R′ = Me) are typical; similar families of curves were obtained for (VII; R = H, R′ = Me, and R = R′ = H).

The enolised cyclic 1 : 3-dione chromophore in (II; R = R′ = Me) showed concentration-dependent absorption in ethanol (Fig. 2);[12] in dilute solution the anion absorption band at 285 mμ (cf. dimedone, 280 mμ) reinforced that due to the substituted coumaranone chromophore, giving a broad peak of high intensity. There was no sharp isosbestic point. Curves for (II; R = H, R′ = Me) (Fig. 3) also showed concentration-dependent absorption in ethanol but in this case the effect was complicated by the presence of the 6-hydroxycoumaranone chromophore. Both triones (II; Me and H, R′ = Me) possessed absorption maxima at 267—275 mμ in ethanol in concentrated solution (cf. dimedone, 255 mμ), in aqueous-ethanolic hydrochloric acid, and in ethanolic McIlvaine buffer pH 2·1, and thus exist in these solvents mainly as the enols (IV; R = Me and H, R′ = H) corresponding to the methyl ether (IV; R = R′ = Me) and not as the enols (I; R = Me and H, R′ = H) corresponding to griseofulvin. After subtraction of absorption due to the coumaranone chromophore, the 1 : 3-dione enol methyl ether chromophore absorbs at 250 mμ in griseofulvin (cf. dimedone methyl ether, 249 mμ) and at 259 mμ in the isomeric (IV; R = R′ = Me). The bathochromic shift in the latter compound is unexpected but may be due to interaction between the two carbonyl groups at the 3- and 2′-positions; Cram and

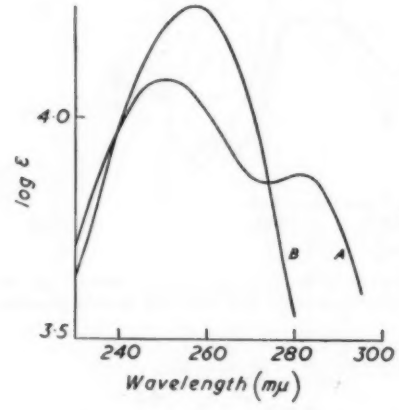


FIG. 4. *Ultraviolet absorption of dimedone.*

(A) In MeOH *containing* 2% *of* HCl. *(B) As (A) but after dilution with an equal volume of water.*

Steinberg[13] have suggested that the anomalous absorption of 1 : 6-dioxo*spiro*[4 : 4]nonane might be due to such an interaction.

In ethanol containing 2% of hydrogen chloride, the triones (II; R = R′ = Me, and R = H, R′ = Me) display absorption almost identical with that of (IV; R = Me, R′ = Et).[3] This result suggests that rapid ethylation of the triones occurs in this solvent. Similarly, dissolution of griseofulvin in methanol containing 2% of hydrogen chloride appears to cause rapid conversion into the isomeric methyl ether (IV; R = R′ = Me) since the absorption spectrum in this solvent is identical with that of (IV; R = R′ = Me) in the same solvent.[2] It is of interest that dimedone is not methylated after three days at room temperature with methanol–2% hydrogen chloride; the absorption (Fig. 4) in this solvent shows reduced intensity at 250 mμ (undissociated enol chromophore) and an absorption maximum at 280 mμ (conjugate acid chromophore), indicating an equilibrium between the undissociated enol and the conjugate acid.[14] On dilution of this solution with water, the band at 280 mμ disappears and the band at 250 mμ increases in intensity.

The absorption data presented for (II; R = R′ = Me), (II; R = H, R′ = Me), and (III; R = H, R′ = Me) correct those published in Parts I[2] and II[4] of this series.

[11] Meek, Turnbull, and Wilson, *J.*, 1953, 2891.
[13] Cram and Steinberg, *J. Amer. Chem. Soc.*, 1954, **76**, 2753.
[14] Eistert, Merbel, and Reiss, *Chem. Ber.*, 1954, **87**, 1513.

Infrared Absorption.—Duncanson, Grove, and Zealley [15] have shown that 4- and 7-hydroxyphthalides can be distinguished by their infrared spectra in dilute solution; the weak intramolecular hydrogen bonding in the 7-hydroxy-derivatives causes a characteristic lowering of the carbonyl frequency by about 20 cm.$^{-1}$. This work has been extended to hydroxycoumaranones where, in model compounds, it was found that a 4-hydroxy-substituent lowers the carbonyl frequency by about 20 cm.$^{-1}$ (Table 2).

Farmer, Hayes, and Thomson [16] have quoted the data for (VII; R = R′ = H; R = H, R′ = Me; and R = Me, R′ = H); these measurements were obtained by us on specimens prepared for this investigation in these laboratories.

The trione (II; R = H, R′ = Me) and acid (III; R = H, R′ = Me) showed carbonyl absorption typical of a 6-hydroxycoumaranone in accord with the assigned structures.

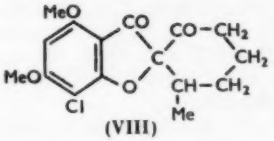
TABLE 2. *Carbonyl stretching frequency of hydroxycoumaranones in chloroform solution.*

Compound	ν (cm.$^{-1}$)	Compound	ν (cm.$^{-1}$)	Compound	ν (cm.$^{-1}$)
VII; R = R′ = H ...	1679	III; R = H, R′ = Me	1708	II; R = H, R′ = Me	1701
VII; R = Me, R′ = H	1682	III; R = R′ = Me ...	1704	II; R = R′ = Me	1701
VII; R = H, R′ = Me	1698			IX	1701
VII; R = R′ = Me ...	1700				

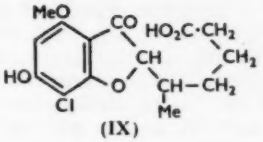
The phenolic acid, obtained [17] by alkaline hydrolysis of the reduction product (VIII) of the isomer (IV; R = R′ = Me) of griseofulvin, is clearly not a 4-hydroxycoumaranone and must be the 6-hydroxy-compound (IX).

Model Compounds.—Although the 6-methyl ether linkage in the diether (II; R = R′ = Me) is readily hydrolysed by aqueous alkali, it is stable to much more vigorous treatment with mineral acid. Thus the ether was recovered in 55—70% yield after 24 hours' refluxing with 6N-sulphuric acid, and no phenolic products could be isolated.

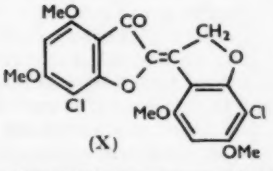
The stability of the methyl ether groups in several model compounds, structurally related to the aromatic ring in griseofulvin, was determined by refluxing with 0·5—3N-sodium hydroxide. All models contained a chloro-substituent since it has been shown [18] that the 6-methoxyl substituent in dechlorogriseofulvin is stable to alkali.



(VIII)



(IX)



(X)

Of the models examined, only (±)-β-(7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-yl)-butyric acid (III; R = R′ = Me) and 7-chloro-4 : 6-dimethoxycoumaranone possessed methyl ether linkages which were split with aqueous alkali. The former, whose synthesis will be described in a later paper, gave the corresponding (±)-6-hydroxy-derivative (III; R = H, R′ = Me). The latter yielded the self-condensation product (X) in high yield together with uncharacterised phenolic material (5%); more vigorous treatment with aqueous alkali caused extensive decomposition without increasing the yield of phenolic material.

The following derivatives of acetophenone were unaffected: 3-chloro-4-methoxy, 5-chloro-2-methoxy, 3-chloro-2 : 4 : 6-trimethoxy, and 3-chloro-2-hydroxy-4 : 6-dimethoxy. The last mentioned compound was prepared by a Friedel–Crafts reaction between 2-chloro-3 : 5-dimethoxyphenol and acetyl chloride; the methyl ether, 3-chloro-2 : 4 : 6-trimethoxy-acetophenone, was prepared by methylation with methyl iodide and potassium carbonate.

[15] Duncanson, Grove, and Zealley, *J.*, 1953, 1331.
[16] Farmer, Hayes, and Thomson, *J.*, 1956, 3600.
[17] Mulholland, *J.*, 1952, 3994.
[18] MacMillan, *J.*, 1953, 1697.

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Among other model compounds methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate was quantitively hydrolysed by alkali to the corresponding benzoic acid. 8-Chloro-5 : 7 : 4′-trimethoxyflavone, suggested by Dr. W. D. Ollis, Bristol University, as a possible model, was split into 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid and 4-methoxyacetophenone. The flavone was prepared from buddleoflavanoloside by hydrolysis to acacetin [19] followed successively by chlorination and methylation.

Attempts to prepare 3 : 5-dichloro-2 : 4 : 6-trimethoxyacetophenone by a Friedel–Crafts reaction on 2 : 4-dichloro-1 : 3 : 5-trimethoxybenzene were unsuccessful. From reactions in carbon disulphide 3 : 3′-dichloro- and 3 : 3′ : 5-trichloro-2 : 2′ : 4 : 4′ : 6 : 6′-hexamethoxydiphenyl were obtained (the latter by methylation of a phenolic fraction), together with the acetate of 2 : 6-dichloro-3 : 5-dimethoxyphenol.[5]

It is notable that the 2-hydroxy-derivative of (III; R = R′ = Me) which exists in alkaline solution in the open-chain 1 : 2-dione form does not suffer hydrolysis of the 6-methyl ether linkage with aqueous alkali although it undergoes a benzilic acid rearrangement. This fact, and the above model experiments show that an aryl methyl ether linkage, situated *para* to the carbonyl group in a 7-chlorocoumaranone is readily hydrolysed by dilute aqueous alkali whereas a methoxyl group similarly situated in an acetophenone is stable. Substitution of the coumaranone in the 2-position prevents preferential self-condensation.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney. M. p.s are corrected. In chromatography, B.D.H. alumina was rendered alkali-free (pH 4) and activated at 250°/15 mm. Ultraviolet light absorption was measured with a Unicam S.P. 500 spectrophotometer. The infrared spectra were measured with a Grubb-Parsons S 3A spectrometer fitted with a rock-salt prism.

Ethylation of 7-Chloro-6-hydroxy-4-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione (II; R = H, R′ = Me).—The trione (1·17 g.), suspended in ethanol (15 ml.), was treated overnight with diazoethane (from 10 g. of 4-ethylamino-4-methyl-3-nitrosopentan-2-one) in ether (200 ml.). The recovered gum in benzene (30 ml.) was adsorbed on alumina (28 × 1·5 cm.), and the band of general adsorption (blue in ultraviolet light) was eluted with benzene. The recovered colourless gum, on treatment with ether, deposited *7-chloro-6 : 2′-diethoxy-4-methoxy-6′-methylgris-2′-en-3 : 4′-dione* (I; R = R′ = Et) which crystallised from ethanol in needles (420 mg.), m. p. 174—175° (Found : C, 59·9; H, 5·4; Cl, 8·9; OAlk as OMe, 24·5. $C_{19}H_{21}O_6Cl$ requires C, 59·9; H, 5·6; Cl, 9·3; OAlk as OMe, 24·4%), $\lambda_{max.}$ (in EtOH) ~323, 292, ~255, 235 mμ (log ε 3·75, 4·36, 4·18, 4·34 respectively). The infrared spectrum of a " Nujol " mull showed absorption max. at 1705 and 1654 cm.$^{-1}$ in the double-bond stretching region.

The ether mother-liquors, cooled in acetone–solid carbon dioxide, deposited *7-chloro-6 : 4′-diethoxy-4-methoxy-6′-methylgris-3′-en-3 : 2′-dione* (IV; R = R′ = Et) which crystallised from ethanol in needles (460 mg.), m. p. 205° (Found : C, 59·4; H, 5·3; OAlk as OMe, 25·4%), $\lambda_{max.}$ (in EtOH) ~320, 292, 260, 236 mμ (log ε 3·78, 4·23; 4·23; 4·30 respectively).

In some preparations the diethyl ether (IV; R = R′ = Et) could not be obtained solid.

Oxidation of 7-Chloro-6 : 2′-diethoxy-4-methoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R′ = Et).—To the diethyl ether (250 mg.) in acetone (40 ml.) was added powdered potassium permanganate (1·0 g.). After 16 hr. at room temperature, the precipitated manganese salts were collected, washed with acetone, and extracted with dilute aqueous ammonia. Acidification of the alkaline extract gave *3-chloro-4-ethoxy-2-hydroxy-6-methoxybenzoic acid* which crystallised from ethyl acetate in needles (11 mg.), m. p. 179—181° (decomp.) (Found : C, 48·4; H, 4·5. $C_{10}H_{11}O_5Cl$ requires C, 48·7; H, 4·5%). The methyl ether methyl ester, obtained with diazomethane, crystallised from diethyl ether in plates, m. p. 120—122° and was identical (mixed m. p. and infrared spectrum) with a synthetic specimen of *methyl 3-chloro-4-ethoxy-2 : 6-dimethoxybenzoate*, prisms, m. p. 122—124° [from light petroleum (b. p. 40—60°)] (Found : C, 52·8; H, 5·3; Cl, 12·8. $C_{12}H_{15}O_5Cl$ requires C, 52·5; H, 5·5; Cl, 12·9%), prepared by treatment of methyl 3-chloro-4-hydroxy-2 : 6-dimethoxybenzoate with diazoethane.

4 : 6-Dihydroxycoumaranone, prepared by the method of Drumm, MacMahon, and Ryan,[20]

[19] Baker, Hemming, and Ollis, *J.*, 1951, 691.
[20] Drumm, MacMahon, and Ryan, *Proc. Roy. Irish Acad.*, 1924, **36**, 149.

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had m. p. 255° (decomp.), p*K* 6·2. It gave a reddish colour with methanolic titanous chloride.

6-Hydroxy-4-methoxycoumaranone was prepared by methylation of 4 : 6-dihydroxycoumaranone as described by Geissman and Hinreiner.[8] The product, crystallised from dioxan, had m. p. 299—300°, p*K* 6·0 (Geissman and Hinreiner recorded m. p. 290—292°; Gruber and Horvarth [9] give m. p. 262—269°) (Found : C, 59·9; H, 4·5. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5%). It gave no colour with methanolic titanous chloride and gave a violet colour with concentrated nitric acid.

4-*Hydroxy*-6-*methoxycoumaranone*.—(a) 2 : 6-*Diacetoxy*-4-*methoxyacetophenone*. 2 : 6-Dihydroxy-4-methoxyacetophenone [7] (4·0 g.) and acetic anhydride (20 ml.) were heated under reflux for 24 hr. then poured into ice-water. An ethereal extract of the precipitated solid was washed with 0·25N-sodium hydroxide and with water; concentration of the dried solution, after treatment with charcoal, gave the *diacetate* (4·4 g.), m. p. 73—75°. It formed prisms m. p. 76°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 58·5; H, 5·4. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%).

(b) 2 : 6-*Diacetoxy*-ω-*bromo*-4-*methoxyacetophenone*. The above acetate (6·0 g.) in carbon disulphide (350 ml.) was stirred at room temperature during the addition (5 hr.) of bromine (3·74 g.) in carbon disulphide (62 ml.). The product separated towards the end of the addition and after being kept at 0° for 0·5 hr. was collected. The filtrate, to which ether was added, was washed with water and the dried solution was evaporated to dryness *in vacuo* at low temperature. The residual *bromo-compound* was washed with a little ether, combined with the first crop, and crystallised from benzene–light petroleum (b. p. 60—80°) in needles (5·2 g.), m. p. 94—96°. A pure specimen had m. p. 96—97° (Found : C, 44·95; H, 4·0; Br, 23·05. $C_{13}H_{13}O_6Br$ requires C, 45·2; H, 3·8; Br, 23·2%).

(c) ω-*Bromo*-2 : 6-*dihydroxy*-4-*methoxyacetophenone*. The foregoing bromo-compound (3·8 g.) in ethanol (80 ml.) was heated under reflux for 20 min. with 16% aqueous hydrogen bromide (100 ml.). After dilution with water, the mixture was concentrated *in vacuo* at room temperature. The crude product (2·7 g.) separated as a yellow gum (which soon solidified), followed by pale yellow needles of almost pure *product*. The latter crystallised from benzene in almost colourless needles, m. p. 139·5—140·5 (decomp.) (Found : C, 42·0; H, 3·7; Br, 30·5. $C_9H_9O_4Br$ requires C, 41·4; H, 3·5; Br, 30·6%).

(d) 4-*Hydroxy*-6-*methoxycoumaranone*. The crude dihydroxy-compound (2·5 g.) and sodium acetate trihydrate (2·5 g.) in ethanol (110 ml.) were heated under reflux for 1 hr. The residue obtained on evaporation *in vacuo* was washed with water, dried, and sublimed *in vacuo*, giving 4-hydroxy-6-methoxy-coumaranone as a colourless solid (0·97 g.). It crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 144°, p*K* 6·64 (Found : C, 60·0; H, 4·6; OMe, 16·8. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5; 1 OMe, 17·2%). Methylation, with diazomethane, gave 4 : 6-dimethoxycoumaranone, m. p. and mixed m. p. 136—138°.

4-Hydroxy-6-methoxycoumaranone was slightly soluble in cold dilute sodium hydroxide but readily soluble on heating, the sodium salt separating on cooling. It gave a brown colour with methanolic ferric chloride, a red colour with methanolic titanous chloride, and a violet colour with concentrated nitric acid. The 2 : 4-*dinitrophenylhydrazone*, crystallised from nitrobenzene, decomposed at 220° (Found : C, 49·9; H, 3·4; N, 15·1. $C_{15}H_{12}O_7N_4$ requires C, 50·0; H, 3·4; N, 15·55%). A crystalline benzylidene derivative could not be prepared.

Balakrishna *et al.*[10] reported the preparation of 4-hydroxy-6-methoxycoumaranone by partial methylation of the parent 4 : 6-dihydroxy-compound and gave m. p. 147—148°; in our hands this preparation was unsuccessful.

3-*Chloro*-2-*hydroxy*-4 : 6-*dimethoxyacetophenone* (With Mr. A. W. Dawkins).—A mixture of 2-chloro-3 : 5-dimethoxyphenol (25 g.), redistilled nitrobenzene (35 g.), and acetyl chloride (20 g.) was treated with powdered aluminium chloride (35 g.) during 1 hr. with cooling, then kept at room temperature for 72 hr. and diluted with water (250 ml.), followed by concentrated hydrochloric acid (30 ml.). After removal of the nitrobenzene in steam the black solid was collected and triturated with ether. The yellow powder (29 g.) so obtained crystallised from a large volume of methanol, yielding the required *acetophenone* as yellow needles (26·5 g.), m. p. 191—192° (Found : C, 52·1; H, 4·5; Cl, 15·4. $C_{10}H_{11}O_4Cl$ requires C, 52·1; H, 4·8; Cl, 15·4%). The phenol gave a brown colour with ethanolic ferric chloride and a green colour with methanolic titanous chloride. The infrared spectrum showed an absorption band at 1625 cm.$^{-1}$ due to the chelated and unsaturated carbonyl group.

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The *methyl ether*, prepared by boiling the phenol (100 mg.) in acetone (10 ml.) for 6 hr. with methyl iodide (0·5 ml.) and potassium carbonate (1·0 g.) and pouring the mixture into water (10 ml.), was obtained in colourless needles (90 mg.) and was purified by sublimation at 70°/10^{-2} mm.; it had m. p. 74° (Found: C, 54·4; H, 5·25; Cl, 13·9; OMe, 33·05. $C_{11}H_{13}O_4Cl$ requires C, 54·0; H, 5·3; Cl, 14·5; 3OMe, 38·0%). It gave no colour with methanolic titanous chloride.

8-Chloro-5 : 7 : 4′-trimethoxyflavone (With Miss M. T. KENNEDY).—5 : 7-Dihydroxy-4′-methoxyflavone (200 mg.; m. p. 263°; prepared by hydrolysis of buddleoflavanoloside [19]) in acetic acid (75 ml.) was treated with sulphuryl chloride (164 mg.) in acetic acid (15 ml.) (immediate separation of yellow needles). After 1 hr. at room temperature, the *8-chloro-derivative* (180 mg.) was collected and recrystallised from ethanol in yellow needles, m. p. 306—308° (Found: C, 60·7; H, 4·05; Cl, 10·3. $C_{16}H_{11}O_5Cl$ requires C, 60·3; H, 3·5; Cl, 11·1%). The acetic acid mother-liquors, after 18 hr. at 0°, deposited a pale yellow *substance* (60 mg.), m. p. 246° (Found: C, 46·95; H, 2·7; Cl, 25·4. $C_{16}H_9O_5Cl_3,H_2O$ requires C, 47·3; H, 2·7; Cl, 26·2%).

The foregoing 8-chloro-derivative (160 mg.) in acetone (75 ml.) was heated under reflux for 16 hr. with methyl iodide (4 ml.) and potassium carbonate (10 g.). The precipitate obtained on pouring the mixture into water was collected and recrystallised (charcoal) from methanol in cream-coloured needles (100 mg.), m. p. 218—220°, of *8-chloro-5 : 7 : 4′-trimethoxyflavone* (Found: C, 62·5; H, 4·3; Cl, 9·9. $C_{18}H_{15}O_5Cl$ requires C, 62·3; H, 4·3; Cl, 10·2%).

Attempted Nuclear Acetylation of 2 : 4-Dichloro-1 : 3 : 5-trimethoxybenzene (With Miss D. ISMAY).—(*a*) The dichloro-compound was recovered unchanged after treatment with acetyl chloride and concentrated sulphuric acid in ether at room temperature, with acetyl chloride and aluminium chloride in boiling carbon disulphide for 12 hr., and with acetic anhydride and aluminium chloride in boiling ether for 2 hr. Treatment with acetic anhydride and aluminium chloride in nitrobenzene at 200° led to extensive decomposition.

(*b*) Powdered aluminium chloride (3·34 g., 0·025 mole) was added to the dichlorotrimethoxybenzene (2·38 g., 0·01 mole) in carbon disulphide (25 ml.); acetic anhydride (1·02 g., 0·01 mole) was added dropwise to the boiling solution and heating under reflux was continued for 2 hr. The solvent was removed by distillation and the brown residue was treated with ice and concentrated hydrochloric acid. An ether extract of the resulting orange solution was extracted with 3N-sodium hydroxide and washed with water. Recovery of the neutral fraction afforded a brown solid which on crystallisation from methanol yielded (1) *3 : 3′-dichloro-2 : 2′ : 4 : 4′ : 6 : 6′-hexamethoxydiphenyl*, needles (70 mg.), m. p. 193—204°, raised by repeated recrystallisation from methanol to 206—208° [Found: C, 53·4; H, 5·2; Cl, 17·4%; *M* (Rast), 382. $C_{18}H_{20}O_6Cl_2$ requires C, 53·6; H, 5·0; Cl, 17·6%; *M*, 403] (no infrared bands attributable to carbonyl groups), and (2) a solid (1·7 g.), m. p. 84—94°, which, after adsorption on alumina (12 × 1·5 cm.) from benzene and elution of the band fluorescing blue in ultraviolet light, yielded *2 : 6-dichloro-3 : 5-dimethoxyphenyl acetate* (710 mg.), needles, m. p. 127—129° (Found: C, 45·4; H, 3·9; Cl, 26·3. $C_{10}H_{10}O_4Cl_2$ requires C, 45·3; H, 3·8; Cl, 26·8%). It was identical (mixed m. p.) with a specimen prepared from 2 : 6-dichloro-3 : 5-dimethoxyphenol [6] with acetic anhydride and pyridine. The infrared spectrum showed an absorption band at 1780 cm.$^{-1}$ characteristic of a phenyl acetate.

The alkaline extract on acidification gave a solid (70 mg.), m. p. 150—173°, which was combined with a solid (60 mg.) obtained by ether-extraction of the mother-liquors and was methylated with diazomethane, giving *3 : 3′-dichloro-2 : 2′ : 4 : 4′ : 6 : 6′-hexamethoxydiphenyl* (85 mg.), m. p. and mixed m. p. 201—203°, after crystallisation from methanol.

(*c*) When experiment (*b*) was repeated with 10 g. of the dichloro-compound the neutral fraction (5·0 g.) had m. p. 100—109°. Recrystallisation from methanol gave pale yellow needles (4·1 g.), m. p. 112—127°, which were adsorbed on alumina (18 × 1·5 cm.) from a benzene solution (20 ml.). Elution of the lowest band (mauve fluorescence in ultraviolet light) with benzene and recovery yielded 2 : 6-dichloro-3 : 5-dimethoxyphenyl acetate (2·94 g.), m. p. 115—121° raised by two recrystallisations followed by sublimation at 60°/10^{-3} mm. to 127—129°.

The alkali-soluble fraction, on trituration with methanol, gave a solid, m. p. 182—189°, which with diazomethane yielded *3 : 3′ : 5-trichloro-2 : 2′ : 4 : 4′ : 6 : 6′-hexamethoxydiphenyl*, prisms (from ethyl acetate), m. p. 176—179° [Found: C, 49·6; H, 4·25; Cl, 24·2%; *M* (Rast), 414. $C_{18}H_{19}O_6Cl_3$ requires C, 49·4; H, 4·4; Cl, 24·3%; *M*, 438]. The infrared spectrum showed no bands due to carbonyl or hydroxyl groups.

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Alkaline Hydrolysis Experiments with Model Compounds.—(*a*) 3-Chloro-4-methoxyacetophenone,[21] m. p. 71—73°, was recovered in 97% yield after treatment with boiling 0·5N-sodium hydroxide for 5 hr.

(*b*) 5-Chloro-2-methoxyacetophenone, prepared by Wittig's method,[22] had m. p. 34°. The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 226°, from benzene (Found : C, 49·3; H, 3·6; N, 15·7. $C_{15}H_{13}O_5N_4Cl$ requires C, 49·4; H, 3·6; N, 15·4%). The acetophenone was recovered in 95% yield after 5 hours' boiling with 0·5N-sodium hydroxide.

(*c*) Methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate (100 mg.) was heated under reflux for 5 hr. with 0·5N-sodium hydroxide. Acidification afforded 3-chloro-2 : 4 : 6-trimethoxybenzoic acid (80 mg.), needles, m. p. 186—188° (decomp.) (from aqueous methanol) (Found : C, 48·5; H, 4·6. Calc. for $C_{10}H_{11}O_5Cl$: C, 48·8; H, 4·5%).

(*d*) 3-Chloro-2-hydroxy-4 : 6-trimethoxyacetophenone (104 mg.) was heated under reflux for 5 hr. with 0·5N-sodium hydroxide in a stream of nitrogen. Acidification and recovery of the precipitated solid gave starting material (101 mg.), m. p. 189—192°. Recrystallisation from ethanol gave needles (94 mg.), m. p. and mixed m. p. 190—192°.

(*e*) 3-Chloro-2 : 4 : 6-trimethoxyacetophenone (100 mg.) was treated with 0·5N-sodium hydroxide (10 ml.) as in (*d*). Filtration gave starting material (75 mg.), m. p. and mixed m. p. 73°.

After 3 or 36 hours' boiling with 3N-sodium hydroxide recovery was 35% or 5% respectively. No alkali-soluble material was obtained in the former case, while in the latter, 25% of an intractable solid, m. p. >300°, was isolated.

(*f*) 8-*Chloro*-5 : 7 : 4′-*trimethoxyflavone*. (i) The flavone (60 mg.) and 0·5N-sodium hydroxide (25 ml.) were heated under reflux for 6 hr. Acidification of the filtrate with 3N-hydrochloric acid, after removal of some starting material, gave a yellow solid (6 mg.) which crystallised from methanol (charcoal) in colourless needles, m. p. and mixed m. p. with 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, 210°.

Extraction of the acidic mother-liquors with ether and recovery gave a brown oil which with Brady's reagent yielded an orange solid, m. p. 218°, raised by recrystallisation from ethanol to 220° and undepressed on admixture with 4-methoxyacetophenone 2 : 4-dinitrophenylhydrazone.

(ii) The flavone (52 mg.) in methanol (30 ml.) containing 0·5N-sodium hydroxide (50 ml.) was heated under reflux for 6 hr. Working up as before yielded 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, m. p. 216—218°, identified by infrared spectrum and mixed m. p. (Found : C, 46·9; H, 4·3. Calc. for $C_9H_9O_5Cl$: C, 46·5; H, 3·9%), and 4-methoxyacetophenone 2 : 4-dinitrophenylhydrazone, m. p. 212°.

(*g*) 7-Chloro-4 : 6-dimethoxycoumaranone [23] (100 mg.), suspended in 0·5N-sodium hydroxide (10 ml.), was heated under reflux for 3 hr. in a stream of nitrogen. After cooling to 0°, the solid was collected and the filtrate which darkened rapidly in air was acidified with concentrated hydrochloric acid and extracted with ether. The neutral solid (75 mg.) was adsorbed on alumina (3 × 1·5 cm.) from benzene and the least strongly adsorbed band which fluoresced bright yellow in ultraviolet light was collected. Recovery gave a colourless solid (26 mg.) which crystallised from benzene in prisms, m. p. 249—250°, of 7-*chloro*-2-(7-*chloro*-4 : 6-*dimethoxycoumaran*-3-*ylidene*)-4 : 6-*dimethoxycoumaranone* (Found : C, 55·0; H, 3·5. $C_{20}H_{16}O_7Cl_2$ requires C, 54·7; H, 3·7%), $\lambda_{max.}$ (in EtOH) 326, 287·5, 263·5, 239 mμ (log ε 3·55, 4·13, 4·12, 4·21). The remaining yellow bands, on elution with benzene–methanol (99 : 1), gave intractable orange gums (3·4 mg.)

The ether extract (10 mg.), a brown amorphous material, was dissolved in benzene (30 ml.) and chromatographed on alumina (3 × 1·5 cm.). A colourless band, fluorescing dark blue in ultraviolet light, was eluted with benzene and furnished orange prisms (1 mg.), m. p. 288—290° (decomp.) (from benzene–methanol). A yellow band with a yellow fluorescence in ultraviolet light, eluted with benzene–methanol (99 : 1), gave yellow prisms (5 mg.), m. p. 294—295°, of a *phenol* [Found : C, 48·9; H, 3·6; OMe, 9·8. $C_{18}H_{16}O_9Cl_2$ ($C_{18}H_{12}O_7Cl_2,2H_2O$) requires C, 48·4; H, 3·6; 2OMe, 13·9%]; this gave a positive Millon test but no colour with methanolic ferric or titanous chlorides.

Similar results were obtained by heating under reflux for 8—12 hr. with N-sodium hydroxide

[21] Nguyen-Hoan and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1363.
[22] Wittig, *Ber.*, 1924, **57**, 88.
[23] MacMillan, Mulholland, Dawkins, and Ward, *J.*, 1954, 429.

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in the presence or absence of ethanol. Boiling with 3N-sodium hydroxide for 8 hr. led to extensive decomposition.

(*h*) (±)-β-(7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-yl)butyric acid (234 mg.) in 3N-sodium hydroxide (10 ml.) was heated under reflux for 4 hr. in a current of nitrogen. The cooled solution was filtered from gelatinous material and acidified at 0°. After 24 hr. the cream-coloured solid (123 mg.) was collected and crystallised twice from ethyl acetate, giving (±)-β-(*7-chloro-6-hydroxy-4-methoxy-3-oxocoumaran-2-yl)butyric acid* as colourless ill-defined prisms, m. p. 212—214° (decomp.) (Found : C, 51·9; H, 4·4; Cl, 11·1. $C_{13}H_{13}O_6Cl$ requires C, 51·9; H, 4·3; Cl, 11·8%). Ferric chloride and titanous chloride tests were negative.

We are indebted to Dr. W. D. Ollis for a gift of buddleoflavanoloside.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, AKERS RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, March 11th*, 1957.]

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706. *The Disulphones derived by Oxidation of 2-Amino-2-deoxy-D-glucose Diethyl Dithioacetal Hydrochloride and its N-Acetyl Derivative with Peroxypropionic Acid.*

By L. HOUGH and MAHMOUD I. TAHA.

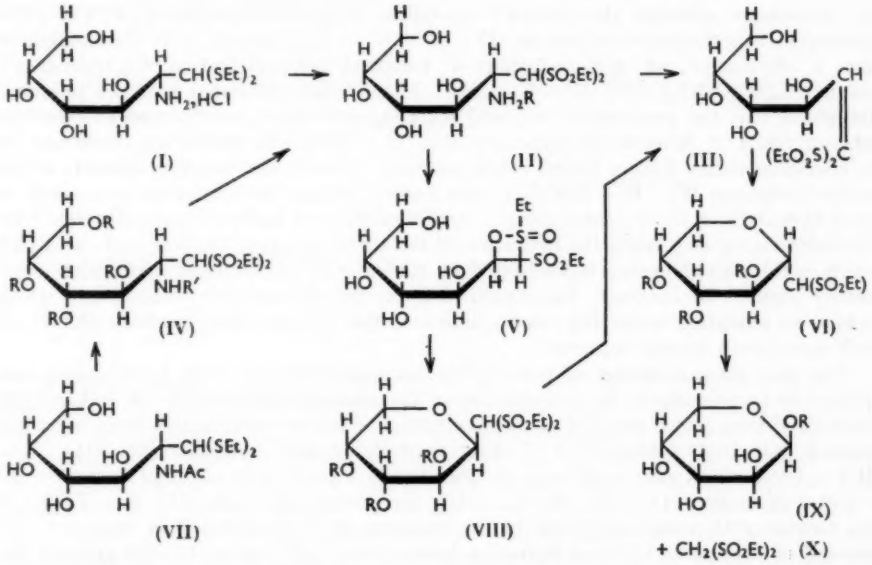
When 2-amino-2-deoxy-D-glucose diethyl dithioacetal was oxidised to the disulphone with peroxypropionic acid at −10°, ammonium chloride was eliminated and cyclisation occurred to give D-*manno*-2 : 6-epoxy-1 : 2-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (diethylsulphonyl-α-D-arabopyranosylmethane). In a similar oxidation of 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal, de-*N*-acetylation occurred with the formation of D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane peroxypropionate. Treatment of this with aqueous ammonia yielded initially a mixture of D-*gluco*- and D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane and D-arabinose, and finally only D-arabinose. Displacement of the diethylsulphonylmethyl group from D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane with sodium methoxide gave methyl β-D-arabopyranoside. The mechanisms of these reactions are discussed.

ALDOHEXOSE DIETHYL DITHIOACETALS are converted by aqueous peroxy-acids [1,2,3] or by hydrogen peroxide containing a little ammonium molybdate,[1,3] into either 1 : 1-diethylsulphonyl-2 : 3 : 4 : 5 : 6-pentahydroxyhexanes or 2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexanes (*e.g.*, VI; R = H), or a mixture of the two. It was of interest, therefore, to study similar oxidations of 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride (I) and its *N*-acetyl derivative (VII) in order to assess the influence of an amino- or acetamido-function on the activated centre at $C_{(2)}$ of the disulphone.

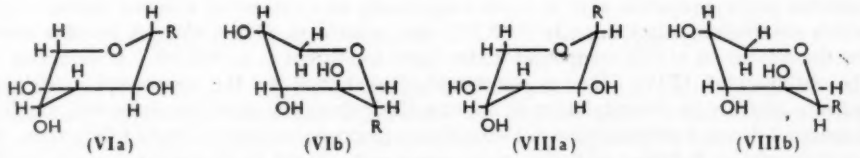
Oxidation of 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride [4] (I) with aqueous peroxypropionic acid at −10° yielded ammonium chloride and a syrup, $[\alpha]_D$ +10°. On paper chromatograms the syrup was indistinguishable from D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane ($[\alpha]_D$ +6·3°) (VI; R = H) derived from the oxidation of D-glucose diethyl dithioacetal and of D-mannose diethyl dithioacetal,[3] and the structure was confirmed by comparison of the crystalline triacetates (VI; R = Ac). The syrup gave a pale yellow colour in dry pyridine, in contrast to the typical magenta or cherry-red colour given by 1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxypent-1-enes.[2] In an excess of dilute aqueous ammonia (pH 10—11), the syrupy disulphone (VI; R = H) was

[1] Zinner and Falk, *Chem. Ber.*, 1955, **88**, 566.
[2] Hough and Taylor, *J.*, 1955, 1212, 3544.
[3] *Idem*, *J.*, 1956, 970.
[4] Whitehouse, Kent, and Posternak, *J.*, 1954, 2315.

cleaved to give D-arabinose (IX; R = H) in high yield and diethylsulphonylmethane (X). In the formation of the cyclic disulphone (VI; R = H), deamination probably took place after the formation of D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane hydrochloride (II; R = HCl) since the analogous 1 : 1-diethylsulphonyl-2 : 3 : 4 : 5 : 6-pentahydroxyhexanes and their penta-*O*-acetyl derivatives readily lose



the elements of water [3] and of acetic acid [5] respectively. The process would be facilitated by the presence of the positive charge on the nitrogen atom and would lead to the formation of the D-*arabo*-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhex-1-ene (III). However, this unsaturated disulphone (III) would cyclise to the 2 : 6-epoxypyranosyl structure (VI; R = H) by the attack of the cationoid $C_{(2)}$ on the terminal primary hydroxyl group.[3] Of the two possible stereoisomeric forms, namely D-*manno*- (VI; R = H) and D-*gluco*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VIII; R = H), only the former was isolated and conformational considerations favour the formation of this configuration. Thus, when the bulky diethylsulphonylmethyl group is assumed to be equatorial, non-bonded interactions would be least in the D-*manno*-stereoisomer (VI; R = H) since



the pyranosyl modification in the 1C chair form [VIa; R = $CH(SO_2Et)_2$] has only one hydroxyl group in an axial position, whereas the D-*gluco*-stereoisomer (VIII; R = H) in the C1 chair form [VIIIb; R = $CH(SO_2Et)_2$] has two axial hydroxyl groups and Δ2 condition.

When 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal [6] (VII) was treated with

[5] MacDonald and Fischer, *J. Amer. Chem. Soc.*, 1952, **74**, 2087.
[6] Hough and Taha, *J.*, 1956, 2042.

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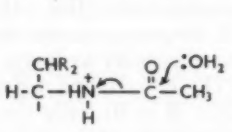
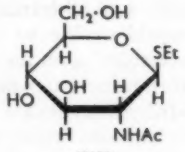
aqueous peroxypropionic acid at −10° a highly crystalline disulphone was obtained. Analysis and molecular-weight estimation [7] of the product indicated that the compound had the molecular formula $C_{13}H_{29}O_{11}NS_2$; *N*-acetyl was absent, which was supported by the formation of a pink colour with ninhydrin on paper chromatograms. These facts, considered together with its highly crystalline nature and neutrality in aqueous solution, suggested that the product was a salt of an organic acid with an amine. On acetylation the disulphone afforded the known [5] crystalline D-*gluco*-2-acetamido-3 : 4 : 5 : 6-tetra-acetoxy-1 : 1-diethylsulphonylhexane (IV; R = R′ = Ac), proving that the disulphone was a derivative of D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxy-hexane ($C_{10}H_{23}O_8NS_2$) (IV; R = R′ = H). These results indicated that the unknown disulphone was the peroxypropionic acid ($C_3H_6O_3$) salt of D-*gluco*-2-amino-1 : 1-diethyl-sulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane (II; R = Et·CO_3H) which was confirmed by its liberating iodine from acidified iodide solution. Clearly the peroxypropionate of the amino-disulphone (II; R = Et·CO_3H) was formed during the oxidation as a result of rapid hydrolysis of the *N*-acetyl group. Acid hydrolysis of amides is normally slow,[8] the rate-determining step being the hydration of the acetyl group of the conjugate acid (XI) which in this case, however, is facilitated by the strongly electrophilic diethylsulphonyl-methyl group. In contrast, 2-acetamido-2-deoxy-β-D-glucopyranosylthioethane [6] (XII) yielded on oxidation under the same conditions, the corresponding sulphone (XIII), no de-*N*-acetylation having occurred.

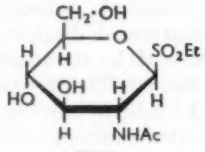
The poor ionic character of peroxypropionic acid compared with hydrochloric acid appears to be responsible for the stability of the amino-disulphone (II; R = Et·CO_3H) under conditions which resulted in the elimination of ammonium chloride from D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane hydrochloride (II; R = HCl). These views gain some support from the fact that, in an attempt to isolate the *N*-acetyl derivative (IV; R = H, R′ = Ac), the peroxypropionate (II; R = Et·CO_3H) was treated with acetic anhydride in the presence of silver acetate [9] in methanol; on removal of silver ions by the addition of hydrochloric acid, the acetylated product was deaminated, ammonium chloride and D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VI; R = H) being formed.



(XI)



(XII)

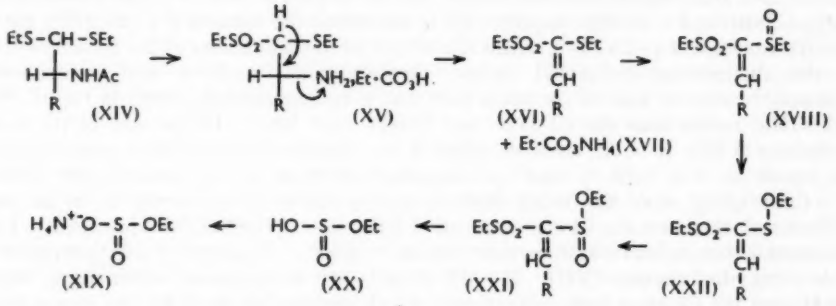


(XIII)

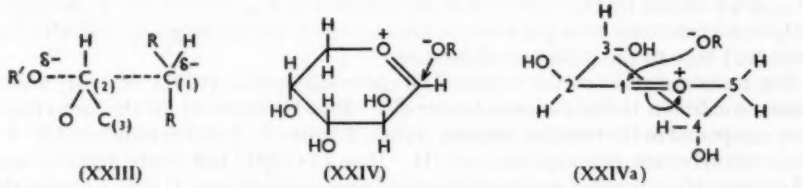
When 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal (VII) was treated with aqueous peroxypropionic acid *at room temperature* an exothermic reaction ensued from which ammonium ethyl sulphite [10] (XIX) was isolated in 87% yield. A possible route for the formation of this compound under these conditions is as follows. If oxidation of the dithioacetal (XIV; R = D-*arabo*tetrahydroxybutyl) to the monosulphone [11] was accompanied by de-*N*-acetylation as appears likely from the above experiments, yielding 2-amino-2-deoxy-1-ethylsulphonyl-1-ethylthio-D-glucose peroxypropionate (XV), then, by analogy with a β-amino-acid, the peroxypropionate would be deaminated easily under acid conditions to give ammonium peroxypropionate (XVII) and the unsaturated mono-sulphone (XVI). Further oxidation of the latter (XVI) would yield initially the 1-sulphone

[7] Menzies and Wright, *J. Amer. Chem. Soc.*, 1921, **23**, 2309, 2314.
[8] Meloche and Laidler, *ibid.*, 1951, **73**, 1712; de Roo and Bruylants, *Bull. Soc. chim. belges*, 1954, **63**, 140.
[9] White, *J.*, 1940, 428.
[10] Divers and Ogawa, *J.*, 1899, **75**, 534.
[11] Bourne and Stephens, *Ann. Rev. Biochem.*, 1956, **25**, 79.

1-sulphoxide derivative (XVIII) in which the ethyl group of the sulphoxide is in an allylic position with respect to the ethylenic group and would, therefore, be expected to migrate under the influence of acids, as a positively charged radical to the sulphoxide oxygen, giving the sulphide (XXII). The sulphur atom would then be oxidised further giving the αβ-unsaturated ester (XXI) which on acid hydrolysis would yield ethyl hydrogen sulphite (XX); this would replace peroxypropionic acid in its ammonium salt (XVII) to form ammonium ethyl sulphite (XIX).



D-*gluco*-2-Amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane peroxypropionate (II; R = Et·CO_3H) was treated with dilute aqueous ammonia (pH 10—11) to give D-arabinose (IX; R = H) in high yield and diethylsulphonylmethane (X). Examination on paper chromatograms indicated that degradation to D-arabinose (IX; R = H) was complete after 5—6 days and that during the reaction at least two intermediates were produced. In order to isolate these intermediates, D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane peroxypropionate (II; R = Et·CO_3H) was allowed to react with dilute aqueous ammonia (pH 10—11) for 24 hr. at room temperature and the mixture was then chromatographed on a column of cellulose : [12] three products were obtained, namely, D-arabinose (18%), D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VI; R = H) (38%), and an unknown syrupy disulphone, $C_{10}H_{20}O_8S_2$ (34%), isomeric with the preceding compound. In dilute aqueous ammonia the unknown compound gave initially a mixture of the D-*manno*-2 : 6-epoxy-



disulphone (VI; R = H) and D-arabinose, but after 6—7 days only D-arabinose was obtained. Paper chromatography with butan-1-ol–pyridine–water as mobile phase caused partial transformation of the unknown compound into D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VI; R = H), showing the lability of the former to base. The unknown disulphone gave only a pale yellow colour in dry pyridine, even after 24 hr., and in aqueous solution was neutral, which suggested [3] that there was no unsaturated linkage within the molecule. The formation of a tri-*O*-acetyl derivative (VIII; R = Ac) indicated the presence of a ring structure involving one of the hydroxyl groups. Periodate oxidation suggested a pyranosyl structure, since the compound consumed two mols. of the

[12] Hough, Jones, and Wadman, *J.*, 1949, 2511; 1950, 1702.

oxidant with the simultaneous liberation of one mol. of acid, thus providing evidence for three free hydroxyl groups attached to contiguous carbon atoms. These facts, considered together with its isomerisation in dilute alkaline solutions to D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VI; R = H), suggested that the unknown disulphone was probably D-*gluco*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (diethylsulphonyl-β-D-arabopyranosylmethane) (VIII; R = H). However, application of Hudson's isorotation rules [13] to the cyclic disulphone ($[M]_D$ +1660°) considered as a D-arabopyranosyl derivative, and to methyl α- and β-D-arabopyranoside [14] ($[M]_D$ −2840° and −40,300° respectively) to determine the value of B (−21,570°), gave a positive value for A (+23,230°), which is contrary to the assignment of the β-configuration to the diethylsulphonylmethyl group. Conformational analysis and experimental evidence,[15] however, lead to the prediction that D-arabopyranoside exists in the 1C (VIa and VIIIa) rather than the C1 (VIb and VIIIb) chair form. In the case of the cyclic disulphone (VIII; R = H), however, where R is a diethylsulphonylmethyl group and is in the β-position, it is unlikely that the compound exists in the 1C conformation [VIIIa; R = $CH(SO_2Et)_2$] since the bulky diethylsulphonylmethyl group would be in an axial position and, therefore, the C1 conformation [VIIIb; R = $CH(SO_2Et)_2$] is favoured. Thus we conclude that methyl D-arabopyranosides and D-*gluco*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VIII; R = H) do not exist in the same conformation, but in the 1C and the C1 chair form respectively, which perhaps accounts for the invalidity of the application of Hudson's rules of isorotation to the latter compound if considered as a D-arabopyranosyl derivative. Similar explanations have been suggested [16,17] for the exceptional character of the rotations of anomeric derivatives having the pyranose ring structure in the mannose, fructose, and sorbose series. The disulphone (VIII; R = H) was obviously formed as a result of deamination of D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane (IV; R = R′ = H) under the influence of base. Under acidic conditions, elimination of the amino-group from D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane salt (II; R = HCl) gave the D-*manno*-2 : 6-epoxy-cyclic disulphone (VI; R = H) as the sole product and deamination probably proceeded by a S_N1 type of mechanism facilitated by the cationoid character of the nitrogen atom. The different behaviour in base can, however, be accounted for by the dissociation from $C_{(2)}$ of the amino-group, which is not cationoid in this case, as a result of participation by one of the neighbouring ethylsulphonyl groups at $C_{(1)}$ with formation of the cyclic intermediate (V). Subsequent cyclisation will proceed with retention of configuration at $C_{(2)}$ since attack by the hydroxyl group attached to $C_{(6)}$ to form the 2 : 6-epoxy-cyclic disulphone could only take place at the side to which the amino-group was attached and would lead only to the D-*gluco*-configuration.

The transformation of the D-*gluco*-2 : 6-epoxy-disulphone (VIII; R = H) under mild alkaline conditions to the D-*manno*-isomer (VI; R = H) accounts for the formation of the latter compound in the reaction between D-*gluco*-2-amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane peroxypropionate (II; R = Et·CO_3H) and dilute aqueous ammonia and presumably proceeded *via* the unsaturated acyclic disulphone (III) by β-elimination and addition. The opening of the pyranose ring under basic conditions would be facilitated by the tendency of the hydrogen atom at $C_{(1)}$ to ionise as a result of the electron-attracting effect of the diethylsulphonyl groups. Subsequent recyclisation would undoubtedly be in favour of the formation of the D-*manno*-2 : 6-epoxy- (VI; R = H) rather than the D-*gluco*-isomer (VIII; R = H) since the former has the least number of non-bonded interactions. Paper chromatography revealed that in dilute aqueous ammonia the transformation of

[13] Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66.
[14] *Idem, ibid.*, 1925, **47**, 265.
[15] Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 107.
[16] Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 1424; 1939, **61**, 2972.
[17] Pacsu, *ibid.*, 1939, **61**, 2669.

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D-*gluco*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (VIII; R = H) into the D-*manno*-isomer was fast (less than 24 hr.) compared with the formation of D-arabinose which required 6—7 days to be complete; after 5 hr. no arabinose was present, but much of the D-*gluco*-disulphone (VIII; R = H) was converted into the D-*manno*-isomer (VI; R = H). These observations, and the fact that the D-*manno*-isomer (VI; R = H) was not transformed in dilute aqueous ammonia into the D-*gluco*-isomer (VIII; R = H) but was degraded directly to D-arabinose, suggested that the degradation of the D-*gluco*-2 : 6-epoxy-disulphone (VIII; R = H) proceeded *via* the D-*manno*-isomer (VI; R = H).

Previous results [3] suggested that cleavage of the cyclic disulphone (VI; R = H) occurs directly by a hydroxyl-ion attack at the cationoid $C_{(2)}$ of the 2 : 6-epoxy(pyranosyl)-ring with a resultant elimination of diethylsulphonylmethane (X) rather than *via* the saturated disulphone $\{HO{\cdot}H_2C{\cdot}[CH(OH)]_4{\cdot}CH(SO_2Et)_2\}$ by addition of the elements of water across the double bond in (III). Further support for the former mechanism was obtained by reaction of D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (diethylsulphonyl-α-D-arabopyranosylmethane) (VI; R = H) with sodium methoxide in methanol from which crystalline methyl β-D-arabopyranoside was obtained in 33% yield; paper chromatography indicated the presence of starting material (VI; R = H) and the absence of 1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxy-2-methoxy-hexane $\{HO{\cdot}H_2C{\cdot}[CH(OH)]_3{\cdot}CH(OMe){\cdot}CH(SO_2Et)_2\}$ and other isomers of methyl arabinosides. The formation of this arabopyranoside (IX; R = Me) confirms the assignment of the pyranose structure to the cyclic sulphone. Since the reaction occurred with complete inversion to give the β-methyl compound (IX; R = Me), the bimolecular mechanism is favoured, although the S_N1 mechanism cannot be overlooked in view of the recent investigations of the *O*-acylglycosyl halides. A bimolecular displacement reaction (S_N2) would involve a transition state (XXIII) where $C_{(1)}$, $C_{(2)}$, and the attacking hydroxyl (or methoxyl) ion are collinear, and where $C_{(3)}$, $C_{(2)}$, the 2-hydrogen atom, and the oxygen atom of the epoxy-ring are coplanar. During this transition, the 3- and the 4-hydroxyl group are brought further apart where they are *trans*-diequatorial in the case of the D-*manno*-configuration (VIa), but nearer in the case of *trans*-diaxial hydroxyls in the D-*gluco*-isomer (VIIIb), and therefore the formation of the intermediate is more favoured in the case of the cyclic D-*manno*-disulphone (VI; R = H). Similar considerations also apply to an S_N1 mechanism involving participation of the ring-oxygen atom with elimination of the diethylsulphonylmethyl group to form the oxonium ion (XXIV). Formation of D-arabinose (IX; R = H) or methyl D-arabopyranoside [*e.g.*, (IX; R = Me)] would be a result of attack at the anomeric carbon atom by a hydroxyl or methoxyl ion respectively, and conformational considerations indicate that the most likely route would be through the half-chair form (XXIVa). Attack by the hydroxyl or methoxyl ion could then occur either from above the plane of the ring, giving the β-isomer in which two functional groups would be equatorial and two would be axial (VIIIa), or from beneath to give the α-isomer; but the latter process is less likely since it would lead to a conformation in which three substituent groups are axial (VIb).

Experimental

Paper chromatography was carried out at 22° on Whatman No. 1 filter paper by the descending method with (i) butan-1-ol–ethanol–water (40 : 11 : 19 v/v), (ii) butan-1-ol–pyridine–water (10 : 3 : 3 v/v), or (iii) ethyl acetate–acetic acid–water (9 : 2 : 2 v/v) as mobile phase. The separated substances were detected with (*a*) a *ca.* 4% solution of silver nitrate containing excess of ammonia, (*b*) a solution of *p*-anisidine hydrochloride [13] in butan-1-ol–ethanol–water, or (*c*) a solution of *ca.* 1% ninhydrin in butan-1-ol. Solutions were evaporated under reduced pressure. Optical rotations are at *ca.* 20°.

2-*Amino*-2-*deoxy*-D-*glucose Diethyl Dithioacetal Hydrochloride*.—2-Amino-2-deoxy-D-glucose hydrochloride (15 g.) was shaken overnight with fuming hydrochloric acid (50 ml.; saturated at 0°) and ethanethiol (25 g.). The solution was diluted with ethanol (250 ml.), then neutralised

with lead carbonate, and the insoluble lead salts were filtered off and washed with ethanol (200 ml.). Concentration of the combined filtrate and washings yielded a colourless syrup (17 g.) which slowly crystallised. Recrystallisation from ethanol–ether gave needles with m. p. 79—80°, $[\alpha]_D$ −16·0° (*c* 2·5 in H_2O), R_F 0·67 [solvent (iii)] (Found : C, 37·1; H, 7·6; N, 4·1; S, 18·6; Cl, 9·8. Calc. for $C_{16}H_{24}O_4NS_2Cl$: C, 37·4; H, 7·5; N, 4·4; S, 19·9; Cl, 11·1%). Whitehouse, Kent, and Posternak [4] record m. p. 75—76°, $[\alpha]_D$ −18·5° in H_2O. Treatment of 2-amino-2-deoxy-D-glucose hydrochloride with ethanethiol and hydrochloric acid (*d* 1·18) for *ca.* 2 months resulted in a 100% recovery of the starting material (see ref. 18).

Peroxypropionic Acid Oxidation of 2-Amino-2-deoxy-D-glucose Diethyl Dithioacetal Hydrochloride.—The diethyl dithioacetal (5·0 g.) in methanol (50 ml.) was cooled to −10° in acetone–solid carbon dioxide, and an excess of cold aqueous peroxypropionic acid (150% of theory for 4 mols., based on propionic anhydride) [2] was added with shaking. The solution was then set aside at room temperature for 1 hr. During subsequent concentration, ammonium chloride (*ca.* 0·9 g.) separated and was filtered off. Further concentration of the filtrate then gave a brown syrup from which traces of peroxypropionic acid were removed by repeated dissolution in methanol and reconcentration. The syrup was decolorised (charcoal) in hot methanol. Evaporation of the solution yielded a colourless syrup (*ca.* 4·0 g.) of D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane which had $[\alpha]_D$ +10° (*c* 3·8 in H_2O), R_F 0·69 [solvent (iii)] (Found : C, 35·8; H, 6·3. Calc. for $C_{10}H_{20}O_8S_2$: C, 36·1; H, 6·0%). Hough and Taylor [3] record $[\alpha]_D$ +6·3° in H_2O.

D-manno-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane*.—A solution of D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (0·5 g.) in acetic anhydride (5 ml.) containing sulphuric acid (1 drop) was heated at 95—100° for ½ hr., then poured into ice-water; an oily triacetate separated which was extracted into chloroform (2 × 30 ml.), and the extracts were washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Concentration of the chloroform solution than gave a pale yellow syrup (0·46 g.) which crystallised overnight. Recrystallised from methanol–ether, the triacetate had m. p. 128° not depressed on admixture with authentic D-*manno*-3 : 4 : 5-tri-*O*-acetyl-2 : 6-epoxy-1 : 1-diethylsulphonylhexane, $[\alpha]_D$ −7·0° (*c* 3·6 in MeOH) [Found : C, 41·7; H, 5·6; S, 13·3; Ac, 26·95 (corrected [2,3]). Calc. for $C_{16}H_{26}O_{11}S_2$: C, 41·9; H, 5·7; S, 14·0; Ac, 28·1%]. Hough and Taylor [3] record m. p. 125—127°.

Treatment of D-manno-2 : 6-*Epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane with Ammonia*.—The disulphone (1·0 g.) was shaken with dilute aqueous ammonia (20 ml.; pH 10—11) at room temperature. The mixture became pale brown and paper chromatography indicated that reaction was complete in 4—5 days. During this time crystals separated : they (*ca.* 0·4 g.) were filtered off, washed with water, and after recrystallisation from methanol had m. p. 102°, not depressed on admixture with authentic diethylsulphonylmethane. The combined filtrate and washings were concentrated, yielding a brownish syrup (*ca.* 0·5 g.) which was decolorised (charcoal) in hot methanol. Evaporation of this solution yielded a pale yellow syrup which crystallised gradually. Recrystallisation from methanol afforded D-arabinose, m. p. and mixed m. p. 158—159°, $[\alpha]_D$ −100° (equil.; *c* 2·3 in H_2O), R_F 0·13 [solvent (iii)].

Treatment of D-manno-2 : 6-*Epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane with Sodium Methoxide*.—Sodium (*ca.* 0·1 g.) was added to the sulphone (0·3 g.) in methanol (10 ml.) at 0°, and the solution stored in the ice-box for 5 days. Amberlite IR-120 (H) ion-exchange resin (*ca.* 5 g.) was added and the mixture was shaken for 2 hr. The resin was filtered off and washed 5 times with methanol, and the combined filtrate and washings were concentrated, yielding a colourless syrup which when examined on paper chromatograms with spray (*a*) was observed to contain, besides unchanged starting material, a component with R_F 0·41 (solvent iii) indistinguishable from methyl β-arabopyranoside. On storage crystalline methyl β-D-arabopyranoside (0·045 g.) separated and was filtered off and washed several times with acetone. It had m. p. 168°, $[\alpha]_D$ −222° (*c* 1·45 in H_2O), R_F 0·41 (solvent iii). Hudson [14] records m. p. 169°, $[\alpha]_D$ +245·5° in H_2O, for the L-isomer.

Peroxypropionic Acid Oxidation of 2-Acetamido-2-deoxy-D-glucose Diethyl Dithioacetal.—2-Acetamido-2-deoxy-D-glucose diethyl dithioacetal (10 g.) in methanol (50 ml.) was oxidised as for 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride, but at −10°, giving crystalline D-gluco-2-*amino*-1 : 1-*diethylsulphonyl*-3 : 4 : 5 : 6-*tetrahydroxyhexane peroxypropionate* (*ca.* 10 g.) which after two recrystallisations from methanol–ether had m. p. 88—90°,

[14] Wolfrom and Anno, *J. Amer. Chem. Soc.*, 1952, **74**, 6150.

$[\alpha]_D$ +10° (*c* 2·03 in H_2O), R_F 0·57 [solvent (iii)] (Found: C, 35·4; H, 6·8; S, 14·3; N, 3·3%; *M*, 430.[7] $C_{13}H_{29}O_{11}NS_2$ requires C, 35·6; H, 6·7; S, 14·6; N, 3·2%; *M*, 439). The compound oxidised acidic iodide solutions with the liberation of iodine.

Oxidation of 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal (0·6 g.) with aqueous peroxypropionic acid *at room temperature* yielded a crystalline compound (*ca.* 0·2 g.), m. p. 204°, which was identified as ammonium ethyl sulphite [10] according to the following evidence; it sublimed unchanged when heated gradually; with warm aqueous sodium hydroxide, it liberated ammonia and with warm dilute hydrochloric acid liberated sulphur dioxide; a white precipitate, which dissolved in concentrated hydrochloric acid, was obtained when treated with barium chloride solution; it was extremely hygroscopic and unstable in the presence of water (Found: C, 19·0; H, 7·2; N, 10·9; S, 25·4. Calc. for $C_2H_9O_3NS$: C, 18·9; H, 7·1; N, 11·0; S, 25·1%).

D-gluco-2-*Acetamido*-3 : 4 : 5 : 6-*tri*-O-*acetyl*-1 : 1-*diethylsulphonylhexane*.—D-*gluco*-2-Amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane peroxypropionate (0·1 g.) in dry pyridine (2 ml.) was treated with acetic anhydride (2 ml.) as above, yielding the acetate as crystals (0·12 g.) which after recrystallisation from ether had m. p. and mixed m. p. 178°, $[\alpha]_D$ +15° (*c* 3·6 in $CHCl_3$) (Found: C, 42·8; H, 5·8; N, 2·5; S, 10·9; Ac, 37·9. Calc. for $C_{20}H_{33}O_{13}NS_2$: C, 42·8; H, 5·9; N, 2·5; S, 11·4; Ac, 38·5%). McDonald and Fischer [5] record m. p. 176·5—178°, $[\alpha]_D$ +13·5° (in $CHCl_3$).

Reaction of D-gluco-2-*Amino*-1 : 1-*diethylsulphonyl*-3 : 4 : 5 : 6-*tetrahydroxyhexane Peroxypropionate with Dilute Aqueous Ammonia and Separation of the Products*.—The disulphone (7 g.) was treated with dilute aqueous ammonia (100 ml.; pH 10—11) at room temperature, gradually becoming pale yellow. After 24 hr., the solution was concentrated to a pale yellow syrup (*ca.* 5·0 g.) which when examined on paper chromatograms with spray (*a*) was observed to contain at least three products [R_F 0·13, 0·69, 0·86; solvent (iii)]. The syrup was fractionated on a cellulose column, with benzene–ethanol (10 : 1 v/v) as mobile phase. Three fractions were obtained. Fraction 1 gave syrupy D-gluco-2 : 6-*epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane* (*ca.* 1·8 g.), $[\alpha]_D$ +5·0° (*c* 3·4 in H_2O), R_F 0·86 [solvent (iii)] (Found: C, 36·3; H, 6·2. $C_{10}H_{20}O_8S_2$ requires C, 36·1; H, 6·0%). Fraction 2 gave syrupy D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (*ca.* 2·0 g.) with $[\alpha]_D$ +10·0° (*c* 2·3 in H_2O), R_F 0·69 [solvent (iii)]. Fraction 3 gave crystalline D-arabinose (*ca.* 0·4 g.) which after recrystallisation from methanol had m. p. and mixed m. p. 158°, $[\alpha]_D$ −108° (*c* 2·0 in H_2O), R_F 0·13 [solvent (iii)].

D-gluco-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane*.—A solution of D-*gluco*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (fraction 1) (0·5 g.) in acetic anhydride (5 ml.) containing sulphuric acid (1 drop) was heated at 95—100° for ½ hr., then poured into ice-water. The *triacetate* was extracted into chloroform (2 × 20 ml.), and the extracts were washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Concentration of the chloroform solution gave a colourless syrup (0·4 g.), $[\alpha]_D$ +13·3° (*c* 3·0 in MeOH) (Found: C, 42·0; H, 5·5. $C_{16}H_{26}O_{11}S_2$ requires C, 41·9; H, 5·7%).

D-manno-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane*.—D-*manno*-2 : 6-Epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (fraction 2) (0·5 g.) was acetylated as for the D-*gluco*-isomer, yielding crystals (0·45 g.) which after two recrystallisations from methanol–ether had m. p. and mixed m. p. 128°, $[\alpha]_D$ −7·0° (*c* 2·5 in MeOH).

D-*Arabinose from* D-gluco-2 : 6-*Epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane*.—The disulphone (0·5 g.) was kept in dilute aqueous ammonia (10 ml.; pH 10—11) at room temperature for 7 days. Crystals separated, which (*ca.* 0·2 g.) were filtered off, washed with water, and after recrystallisation from methanol had m. p. 102°, not depressed on admixture with authentic diethylsulphonylmethane. The combined filtrate and washings were concentrated, yielding a syrup (*ca.* 0·2 g.) which crystallised. Recrystallisation from methanol gave D-arabinose with m. p. and mixed m. p. 159°, $[\alpha]_D$ −106° (equil.; *c* 3·6 in H_2O), R_F 0·13 [solvent (iii)].

Transformation of D-gluco-2 : 6-*Epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane into the* D-manno-*Isomer*.—The D-*gluco*-disulphone (0·5 g.) was kept in dilute aqueous ammonia (10 ml.; pH 10—11) at room temperature for 24 hr. The solution was concentrated to a pale yellow syrup which consisted mainly of D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane [R_F 0·69 (solvent iii)] with a little of D-arabinose [R_F 0·13 (solvent iii)] as revealed by paper chromatography. The two components were separated by chromatography on filter paper (18·25″ × 22·5″) with solvent (iii), and the D-*manno*-disulphone was extracted from the appropriate part of the chromatogram with hot methanol. The methanol extract

was concentrated to a colourless syrup (*ca.* 0·2 g.) with $[\alpha]_D$ +8·5° (*c* 2·4 in H_2O), R_F 0·69 [solvent (iii)].

D-*manno*-3 : 4 : 5-Tri-*O*-acetyl-2 : 6-epoxy-1 : 1-diethylsulphonylhexane (*ca.* 0·1 g.) was obtained from the triol (0·1 g.) as above and after recrystallisation from acetone–light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 128°, $[\alpha]_D$ −7·2° (*c* 4·0 in MeOH).

2-*Acetamido*-2-*deoxy*-β-D-*glucopyranosylsulphonylethane*.—2-Acetamido-2-deoxy-β-D-glucopyranosylthioethane [6] (1·0 g.) in methanol (20 ml.) was oxidised with peroxypropionic acid (150% of theory for 2 mols., based on propionic anhydride) at −10° as above, giving crystals of the *sulphone* (*ca.* 1·2 g.) which after recrystallisation from methanol–ether had m. p. 172°, $[\alpha]_D$ +42° (*c* 2·4 in H_2O) (Found : C, 40·5; H, 6·6; S, 9·33; N, 4·7; Ac, 14·0. $C_{10}H_{19}O_7NS$ requires C, 40·4; H, 6·4; S, 10·8; N, 4·7; Ac, 14·5%).

Treatment of 2-acetamido-2-deoxy-β-D-glucopyranosylsulphonylethane with dilute aqueous ammonia for 10 days resulted in a 100% recovery of the starting material. The compound was also stable to dilute hydrochloric acid.

Attempted Synthesis of D-gluco-2-*Acetamido*-1 : 1-*diethylsulphonyl*-3 : 4 : 5 : 6-*tetrahydroxyhexane*.—D-*gluco*-2-Amino-1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhexane peroxypropionate (1·0 g.), silver acetate (0·4 g.), and acetic anhydride (1·0 g.) in methanol [9] (20 ml.) were shaken for 3 hr. at room temperature in the dark, then refluxed for 5 min. and filtered hot, and the residue washed with hot water (10 ml.). The combined filtrate and washings were acidified with one drop of concentrated hydrochloric acid and after 2 hr. at room temperature the silver chloride was filtered off. During subsequent concentration ammonium chloride (*ca.* 0·1 g.) separated and was filtered off. Further concentration of the filtrate gave a colourless syrup (0·5 g.) of D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane with R_F 0·69 [solvent (iii)]. Acetylation of this syrup (0·1 g.) gave the triacetate (*ca.* 0·1 g.) which after recrystallisation from methanol–ether had m. p. and mixed m. p. 128°.

Periodate Oxidation.—D-*manno*- and D-*gluco*-2 : 6-Epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexanes were oxidised with sodium metaperiodate at room temperature and the oxidant uptake and acid liberated were determined.[6] The results were as follows :

Compounds		½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	6 hr.	9 hr.
D-*manno*-Disulphone ...	Uptake *	0·66	1·26	1·33	1·60	1·76	1·93	2·05
	Acid	0·22	0·30	0·40	0·66	0·88	0·95	1·0
D-*gluco*-Disulphone	Uptake	0·0	0·40	0·60	0·79	2·0	2·0	2·05
	Acid	0·0	0·2	0·25	0·3	1·0	1·0	1·0

* Moles/mole of compound oxidised.

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707. *Glyceride Synthesis by Direct Esterification.*

By L. HARTMAN.

Glycerides of known structure have been synthesised, without recourse to protecting groups, by making use of differences in reactivity of primary and secondary hydroxyl groups of glycerol. α-Monoglycerides and αα′-diglycerides of a single acid are prepared from acyl chlorides and glycerol in homogeneous chloroform solution obtained with the aid of *NN*-dimethylformamide. Monoacylation was assisted by the use of complexing agents. Diglycerides containing two different acids are obtained by treating a monoglyceride with another fatty acid chloride. Triglycerides containing one unsaturated acid are prepared by a three-stage process.

MOST syntheses of glycerides are based on the use of protecting groups; the present communication reports syntheses based on the difference in reactivity of primary and secondary hydroxyl groups of glycerol. Although the introduction of certain protecting groups, *e.g.*, triphenylmethyl, depends on the greater reactivity of the primary hydroxyl groups, there seems to be no direct experimental proof of the differing reactivities of hydroxyl

groups in glycerol towards fatty acids. Some conclusions can be drawn from the classic work of Menshutkin,[1] who found that the rate of esterification depended on the type of the hydroxyl group: *e.g.*, esterification of ethylene glycol with acetic acid was faster than of propylene glycol, and of glycerol faster than of erythritol or mannitol. The comparative reactivities of primary and secondary hydroxyl groups in glycerol are difficult to establish directly owing to acyl migration in β-monoglycerides and αβ-diglycerides, though this only accentuates the final effect of the α-position's being favoured in comparison with the β-position. Whereas these considerations apply to esterification, as distinct from acylation, the work of Norris and his associates [2] on the reactivity of various alcohols with *p*-nitrobenzoyl chloride has shown that in this respect there is no fundamental difference between the two reactions.

Some use of the different reactivity of α- and β-hydroxyl groups of glycerol has been made in the past. α-Monoglycerides were prepared by Hilditch and Rigg [3] by direct esterification of fatty acids with a large excess of glycerol in phenol, but the products were impure, probably owing to the side reactions with phenol. αα′-Diglycerides were obtained by transesterification of glycerol αα′-disulphate with fatty acids [4] and by esterifying monoglycerides with fatty acid chlorides in the presence of pyridine or with fatty acids in the presence of acid catalysts.[5]

In the present work, fatty acid chlorides were used instead of fatty acids to obtain a greater range of products and better yields. Experimental conditions were established for the preparation of α-monoglycerides, αα′-diglycerides with one and two component acids and triglycerides with one unsaturated acyl group. The preparation of β-monoglycerides and αβ-diglycerides seems to be impracticable by direct esterification without the use of protecting groups.

The reaction of fatty acid chlorides and a large excess of glycerol resulted in formation of α-monoglycerides and some diglycerides. A homogeneous mixture of glycerol and of the solution of fatty acid chlorides in chloroform—an essential feature of the method—was ensured by the use of *NN*-dimethylformamide which seems to be the best cosolvent. To keep diglyceride formation to a minimum it was advisable to reduce the reactivity of one primary hydroxyl group with a suitable chelating agent: 1 mol. of potassium thiocyanate, urethane, or triethyl phosphate proved satisfactory; on the other hand, addition of boric acid resulted in a complete conversion of acid chlorides into acids, and use of urea led to a certain amount of insoluble products.

Diglycerides containing residues of a single acid were prepared by direct acylation of a theoretical quantity of glycerol in homogeneous solution, obtained also with the aid of *NN*-dimethylformamide. Diglycerides containing different acyl groups resulted from the reaction between a monoglyceride and a fatty acid chloride in approximately equimolar proportions. The preparation of such diesters by heating α-monoglycerides with fatty acids in the presence of toluene-*p*-sulphonic acid as catalyst proved impracticable owing to migration of acyl groups.

Of the triglycerides with one unsaturated component acid the three isomeric triglycerides containing stearoyl, palmitoyl, and oleoyl residues are of special interest because of their frequent occurrence in natural products. It seems that the only successful synthesis of these glycerides in the past was by Verkade [6] with the aid of triphenylmethyl compounds. They have now been prepared by three-stage direct acylation. In addition, the preparation of glycerol α-laurate α′-oleate β-palmitate is reported. In order to introduce the third acyl group in these compounds refluxing of the chloroform solution had to be resorted to since at room temperature the reaction was too slow.

[1] Menshutkin, *Ann. Chim. Phys.*, 1880, **20**, 289; 1881, **23**, 14; *Ber.*, 1880, **13**, 812, 814.
[2] Norris and Ashdown, *J. Amer. Chem. Soc.*, 1925, **47**, 837.
[3] Hilditch and Rigg, *J.*, 1935, 1714.
[4] Grün, *Ber.*, 1905, **38**, 2284.
[5] Malkin, Shurbagy, and Meara, *J.*, 1937, 1409.
[6] Verkade, *Rec. Trav. chim.*, 1943, **62**, 393.

XUM

Experimental

Materials.—Fatty acids and their chlorides. Saturated fatty acids were prepared from commercial samples by fractional distillation and crystallisation of methyl esters, and conversion into free acids. Oleic acid was prepared from olive oil by a similar method and had an iodine value of 90·1 (calc. 89·9) and m. p. 13·2°.

In preparing fatty acid chlorides the chief aim was to dispense with the time-consuming distillation of crude products. In the case of saturated fatty acids this was achieved by refluxing the acids for 2 hr. with an equal weight of thionyl chloride previously distilled over quinoline and linseed oil.[7] The acyl chlorides remaining after the removal of the excess of reagent *in vacuo* were pale and were used immediately after preparation.

A pale oleoyl chloride could not be obtained in this way, and therefore oleic acid was refluxed with an equal weight of oxalyl chloride in light petroleum for 2 hr., which resulted in an almost colourless product.

NN-*Dimethylformamide.* This was shaken with anhydrous calcium sulphate and siphoned off when required.

Chloroform. B.P. chloroform was washed with water, dried with calcium chloride and potassium carbonate, and distilled over phosphoric oxide. 0·1 ml. of butanol per l. was added and extended the storage life to several months without interfering appreciably with the esterification of glycerol.

Pyridine. Pyridine was used in preference to quinoline because of the greater ease of its removal with mineral acids. It was dried by refluxing with barium oxide and kept over solid potassium hydroxide.

Glycerol. This was of analytical reagent grade. It was made anhydrous by heating it to 160° before use with continuous stirring. Higher temperatures were avoided in view of the recent findings [8] that dehydration occurs above 170°.

Preparation of α-Monoglycerides.—The preparation of α-monopalmitin is given as an example: Glycerol (18·4 g., 0·2 mole) and potassium thiocyanate (19·5 g., 0·2 mole) were heated in a porcelain dish with stirring to 160° to dehydrate both reagents. The hot mixture was poured into a glass-stoppered bottle and 40 ml. of dry dimethylformamide were added followed by anhydrous pyridine (1·6 g., 0·02 mole) and dry chloroform (30 ml.). To the mixture, cooled to about 10°, palmitoyl chloride (5·5 g., 0·02 mole) in chloroform (10 ml.) was added dropwise with shaking. The initial turbidity usually disappeared after the mixture attained room temperature, otherwise it was removed by addition of chloroform. Next morning ethyl ether (200 ml.) was added and the solution washed 3 times with water to remove potassium thiocyanate, then with 0·5N-hydrochloric acid and with water. The solvents were distilled off. The monopalmitin crystallised from ether (yield, 4·7 g., 71%; m. p. 76·5—77°).

Similar results were obtained by using urethane (19·8 g., 0·2 mole) or triethyl phosphate (36·4 g., 0·2 mole) instead of potassium thiocyanate. In each case the complex-forming agent was heated with glycerol to 160°.

Monolaurin, m. p. 62—63° (64%), monomyristin, m. p. 70° (69%), and monostearin, m. p. 81° (71%), were obtained by a similar procedure, but the amounts of dimethylformamide and chloroform were varied to provide for different solubilities. The α-monoglyceride content in these products was determined by the periodate method of Pohle and Mehlenbacher,[9] suitably modified, and was found to be 98—99%.

αα′-Diglycerides with One Component Acid.—Anhydrous glycerol (0·92 g., 0·01 mole) was dissolved in dimethylformamide (2 ml.), chloroform (15 ml.), and pyridine (5 ml.) in a glass-stoppered bottle. Palmitoyl chloride (5·5 g., 0·02 mole) in chloroform (10 ml.) was added dropwise with shaking and cooling in water. Next day ethyl ether was added and the ethereal solution was washed with 0·5N-sulphuric acid, 5% aqueous potassium carbonate, and water. The product crystallised from alcohol and hexane (3·8 g., 67%; m. p. 73·5—74°) (Found: C, 73·7; H, 12·0. Calc. for $C_{35}H_{68}O_5$: C, 73·9; H, 12·1%).

Distearin was prepared similarly from 0·92 g. of glycerol and 6·05 g. of stearoyl chloride, the yield being 4·5 g. (72%) and the m. p. 80° (Found: C, 74·8; H, 12·4. Calc. for $C_{39}H_{76}O_5$: C, 74·9; H, 12·3%).

[7] Fieser, "Experiments in Organic Chemistry," Heath & Co., New York, 1941, 2nd edn., p. 381.
[8] Hauschild and Petit, *Bull. Soc. chim. France*, 1956, 878.
[9] Pohle and Mehlenbacher, *J. Amer. Oil Chemists' Soc.*, 1950, **27**, 54.

The m. p.s approximate to those reported by Porck and Craig.[10]

αα′-Diglycerides with Two Component Acids.—Glycerol oleate palmitate, oleate stearate, oleate laurate, and palmitate stearate were prepared from corresponding α-monoglycerides and oleoyl or stearoyl chloride. Preparation of the α-palmitate α′-oleate is given as an example: To α-monopalmitin (3·6 g., 0·011 mole) in chloroform (30 ml.) containing pyridine (1 g., 0·012 mole), oleoyl chloride (3 g., 0·01 mole) in chloroform (10 ml.) was added with shaking and cooling. The mixture was left overnight and treated as described for diglycerides with one component acid. After crystallisation from alcohol and 1 : 1 alcohol–light petroleum, 4·1 g. (69%) of diglyceride, m. p. 44·5—45°, were obtained (Found: C, 75·0; H, 12·1%; I val., 42·3. Calc. for $C_{37}H_{70}O_5$: C, 74·7; H, 11·9%; I val., 42·7).

Triglycerides with One Unsaturated Acid Component.—*α-Oleate β-palmitate α′-stearate.* The intermediate products were α-monostearin and the α-oleate α′-stearate prepared as described before. The latter (3·1 g., 0·005 mole) in chloroform (6 ml.) and pyridine (5 ml.) was treated with palmitoyl chloride (1·5 g.) in chloroform (3 ml.) with cooling. The mixture was refluxed on a water-bath for 4 hr., then worked up as for diglycerides and the residue, after the removal of solvents, was crystallised from 4 : 1 acetone–light petroleum at 0° (yield, 3·0 g., 70%; m. p. 40—40·5°) (Found: C, 76·9; H, 12·0; I val., 28·9. Calc. for $C_{55}H_{104}O_6$: C, 76·7; H, 12·2%; I val., 29·5).

α-Oleate α′-palmitate β-stearate. The α-oleate α′-palmitate (3 g., 0·005 mole) was treated with stearoyl chloride (1·7 g.), as above, giving the triglyceride (3·0 g., 70%), m. p. 39—40° (Found: C, 77·0; H, 12·3%; I val., 29·8).

β-Oleate α-palmitate α′-stearate. The α-palmitate α′-stearate (3 g., 0·005 mole) and oleoyl chloride (1·6 g.) yielded triglyceride (3·1 g., 72%), m. p. 37—38° (Found: C, 76·8; H, 12·0%; I val., 29·1).

As reported by Verkade [6] the three isomeric triglycerides when mixed in pairs gave m. p. depressions. Verkade's observation that the first of the three acquires an electrical charge when rubbed was also confirmed.

α-Laurate α′-oleate β-palmitate. The α-laurate α′-oleate (2·7 g., 0·005 mole) was refluxed with palmitoyl chloride (1·5 g.). After the usual purification 2·6 g. (67%) of triglyceride were obtained, having m. p. 29·5° (Found: C, 75·8; H, 11·9%; I val., 33·3. Calc. for $C_{49}H_{92}O_6$: C, 75·7; H, 11·9%; I val., 32·7).

Gratitude is expressed to Dr. E. Marsden, F.R.S., for interest taken in this work and helpful suggestions.

Fats Research Laboratory,
Department of Scientific and Industrial Research,
Wellington, New Zealand. [*Received, March 15th*, 1957.]

[10] Porck and Craig, *Canad. J. Chem.*, 1955, **33**, 1286.

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708. *Further New Tropine Derivatives.*

By R. Foster, P. J. Goodford, and H. R. Ing.

The α-benzylmandelic ester of ψ-tropine and the phenyl-α-2-thienylglycollic and 9-hydroxyfluorene-9-carboxylic esters of tropine have been prepared and tested as spasmolytics. Some new derivatives of the benzilic esters of tropine and ψ-tropine have also been made and tested.

In earlier papers [1,2] the synthesis of the α-benzyl-lactic esters of tropine and ψ-tropine (originally thought to be α-methyltropic esters) was described. In continuation of this work attempts have been made to prepare the tropine and ψ-tropine esters of other disubstituted glycollic acids. The general method of preparation was transesterification, ethyl esters being used because it was found that ethyl benzilate gave yields of 70—80% in the transesterification reaction, whereas with methyl benzilate yields of only 20—30%

[1] Foster and Ing, *J.*, 1956, 938.
[2] *Idem, J.*, 1957, 925.

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were obtained. The reaction was not always successful; thus ψ-tropine α-benzylmandelate was prepared but the corresponding tropine ester could not be obtained. On the other hand, the tropine esters of phenyl-2-thienylglycollic and 9-hydroxyfluorene-9-carboxylic acid were prepared, though in poor yields, but the corresponding ψ-tropine esters could not be obtained.

Ethyl α-benzylmandelate was prepared by the method which Burtner and Cusic [3] devised for the preparation of α-phenyltropic acid, but which Zaugg [4] later proved to give α-benzylmandelic acid by a molecular rearrangement during the reaction of a β-amino-αα-diphenylpropionic ester with nitrous acid.

The benzilic esters of tropine and ψ-tropine were found by Benda and Kraup [5] and by Kreitmair [6] respectively to possess high atropine-like activity. We have included them in our studies and have made and tested their methiodides, ethiodides, and hexamethylene and decamethylene di-iodides.

A summary of the pharmacological results is given in Table 1, in which are included earlier results on the tropine and ψ-tropine esters of α-benzyl-lactic acid and some derivatives of them.

TABLE 1. *Approximate spasmolytic and mydriatic activities of tropine and ψ-tropine esters in terms of atropine sulphate.*

Compound	Spasmolytic activity	Mydriatic activity
Atropine sulphate	1	1
Lachesine	1·5	1
Tropine esters		
α-Benzyl-lactic perchlorate	0·2	0·1
,, methiodide	1	1
,, benzylochloride	0·01	—
Benzilate hydrochloride	1·5 L	0·4
,, methiodide	1	—
,, ethiodide	1	—
Bisbenzilate hexamethylene di-iodide	0·2	0·1
,, decamethylene di-iodide	0·1	—
Phenyl-2-thienylglycollate (free base)	0·7 LP	—
9-Hydroxyfluorene-9-carboxylate (free base)	0·3 L	—
,, ,, ,, methiodide	0·2 LP	—
ψ-Tropine esters		
α-Benzyl-lactate hydrochloride	0·1	0
,, methiodide	1·5	0·25
,, benzylochloride	0·1	—
α-Benzylmandelate (free base)	0·15	—
,, methiodide	0·4	—
Benzilate hydrochloride	0·4	0·2
,, methiodide	1	—
Bisbenzilate hexamethylene di-iodide	0·1	0·03
,, decamethylene di-iodide	0·3	—

L denotes a long-acting but reversible effect.
LP denotes a permanent or very prolonged effect.

It will be seen that both replacement of one phenyl group in tropine benzilate by 2-thienyl and linking of the phenyl groups in the *oo'*-positions reduce spasmolytic activity; in this connexion it has been reported that the phenyl-2-thienylglycollic ester of 2-diethylaminoethanol [7] is 1·5 times as active, but the 9-hydroxyfluorene-9-carboxylic ester [8] one-eighth as active, as the corresponding benzilic ester (rabbit intestine). Lands [7] found that the diphenyl- and the phenyl-2-thienyl-acetic ester of tropine were 6 and 22% as active respectively as atropine (rabbit intestine) so that the introduction of the

[3] Burtner and Cusic, *J. Amer. Chem. Soc.*, 1943, **65**, 262.
[4] Zaugg, *J. Amer. Chem. Soc.*, 1950, **72**, 3001.
[5] Benda and Kraup, *Wien. Klin. Wochenschr.*, 1954, **66**, 445.
[6] Kreitmair, *Klin. Wochenschr.*, 1936, **15**, 676.
[7] Lands, *J. Pharmacol.*, 1951, **102**, 219.
[8] Lands, Hoppe, Lewis, and Ananenko, *ibid.*, 1950, **100**, 19.

α-hydroxy-group into the acyl group of these esters increases activity (cf. Jowett and Pyman [9]) but much more so in the diphenyl- than in the phenyl-2-thienyl-substituted acyl group.

The partially irreversible action of tropine hydroxyfluorenecarboxylate methiodide was unexpected and may be due to a toxic effect upon the ileum since quaternary spasmolytics are usually shorter-acting than their parent tertiary bases. It will be noticed that in accordance with previous experience [10] methiodides are usually more active than their parent bases, the exception in Table 1 being tropine benzilate methiodide.

It is noteworthy that linking of the nitrogen atoms of tropine benzilate by a hexa- or deca-methylene chain produces a striking decrease in spasmolytic activity, whereas Kimura and Unna [11] describe the spasmolytic activity of decamethylenebisatropinium di-iodide as identical with that of atropine.

Experimental

Pharmacology.—Two pharmacological tests were used. Mydriatic activity was estimated on the mouse eye by Pulewka's method [12] as modified by Ing, Dawes, and Wajda.[13] Spasmolytic activity against acetylcholine or carbachol as spasmogenic agents was estimated on isolated guinea-pig ileum. Lachesine (2-benziloylethyldimethylethylammonium chloride [14]) was found to be more convenient than atropine as the standard spasmolytic because it is more rapidly washed out of the isolated ileum and consequently more estimations can be made on one piece of ileum than with atropine. Lachesine was found to be 1·5 times as potent a spasmolytic as atropine.

Table 2. *Derivatives of tropine and ψ-tropine benzilates.*

Ester	M. p.	Solvent	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Tropine benzilate	150° [a]	C_6H_6 or EtOH	$C_{22}H_{25}O_3N$	—	—	—	—
,, hydrochloride	220	PrOH or dioxan	$C_{22}H_{25}O_3N,HCl$	68·2	6·8	68·2	6·7
,, *methiodide*	220	MeOH	$C_{23}H_{28}O_3NI$	56·0	5·6	56·0	5·7
,, *ethiodide*	240	,,	$C_{24}H_{30}O_3NI$	56·8	6·1	56·7	5·9
Bistropine benzilate *hexamethylene di-iodide*	dec. 230—240	EtOH–EtOAc (4 : 1 v/v)	$C_{50}H_{62}NI_2,H_2O$	56·8	6·0	56·8	6·0
Bistropine benzilate *decamethylene di-iodide*	dec. 170	ditto	$C_{54}H_{70}O_6N_2I_2,H_2O$	58·3	6·4	58·2	6·5
ψ-Tropine benzilate	156 [b]	EtOH (70% v/v)	$C_{22}H_{25}O_3N$	—	—	—	—
,, hydrochloride	225 [c]	EtOH–EtOAc (2 : 3 v/v)	$C_{22}H_{25}O_3N{\cdot}HCl$	68·0	6·6	68·2	6·7
,, *methiodide*	240	MeOH	$C_{23}H_{28}O_3NI$	55·7	5·4	56·0	5·7
,, *ethiodide*	240	MeOH	$C_{24}H_{30}O_3NI$	56·5	5·5	56·7	5·9
Bis-ψ-tropine benzilate *hexamethylene di-iodide*	dec. 230—240	MeOH	$C_{50}H_{62}O_2N_2I_2,2H_2O$	55·7	6·0	55·8	6·1
Bis-ψ-tropine benzilate *decamethylene di-iodide*	dec. 195	EtOH (90% v/v)	$C_{54}H_{70}O_6N_2I_2,2H_2O$	57·5	6·5	57·2	6·5 [d]

[a] Hromatka, Csoklich, and Hofbauer [15] give m. p. 152—153°. [b] Wolfes and Hromatka [16] give m. p. 156—158°. [c] Wolfes and Hromatka [16] give m. p. 225—270°. [d] Found: N, 2·4. $C_{54}H_{70}O_6N_2I_2,2H_2O$ requires N, 2·5%.

Chemistry.—All transesterifications were carried out at 120—140° at water-pump pressure for 6 hr. in xylene containing sodium ethoxide (2% of Na).[1, 15]

M. p.s and analyses of tropine and ψ-tropine benzilates and their derivatives are given in Table 2.

[9] Jowett and Pyman, 7th Internat. Congr. Appl. Chem., 1909, IVA, i, 335.
[10] "The Alkaloids," Ed. Holmes and Manske, Academic Press, New York, 1955, Vol. V, pp. 252—257.
[11] Kimura and Unna, *J. Pharmacol.*, 1950, **98**, 286.
[12] Pulewka, *Arch. exp. Path. Pharmak.*, 1932, **168**, 307.
[13] Ing, Dawes, and Wajda, *J. Pharmacol.*, 1945, **85**, 85.
[14] Ford-Moore and Ing., *J.*, 1947, 55.
[15] Hromakta, Csoklich, and Hofbauer, *Monatsh.*, 1952, **73**, 1321.
[16] Wolfes and Hromakta, *Chem. Zentr.*, 1938, I, 2755.

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ψ-Tropine α-benzylmandelate. Ethyl diphenylcyanoacetate [17] (m. p. 59°) was hydrogenated (Raney nickel) in ethanol at room temperature and 6 atm. (60 hr.). After removal of the catalyst and solvent the product was dissolved in dry ether and *ethyl β-amino-αα-diphenylpropionate hydrochloride* precipitated by dry hydrogen chloride (yield, 70%; m. p. 197°). A specimen crystallized twice from ethyl methyl ketone had m. p. 199° (Found: C, 66·6; H, 6·4. $C_{17}H_{19}O_2N$,HCl requires C, 66·8; H, 6·5%). A solution of the crude hydrochloride (45 g.) in 0·5N-sulphuric acid (600 ml.) at 0° was treated dropwise with sodium nitrite (45 g.) in water (100 ml.) with stirring, which was continued without ice-cooling for 3 hr. after the addition of nitrite. Excess of nitrous acid was decomposed by urea, the mixture extracted twice with ether, and the extract washed successively with N-sulphuric acid, aqueous potassium carbonate, and water. The dried extract (Na_2SO_4) gave *ethyl α-benzylmandelate* as a pale yellow oil, b. p. 158°/1 mm. (20 g., 40%) (Found: C, 75·3; H, 6·5. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). Transesterification of this ester with ψ-tropine gave a small yield of acid-soluble oil, which solidified slowly. Two crystallizations from ethyl methyl ketone gave slender needles of *ψ-tropine α-benzylmandelate*, m. p. 135° (Found: C, 75·4; H, 7·4. $C_{23}H_{27}O_3N$ requires C, 75·5; H, 7·4%). The *methiodide*, crystallized from ethanol, had m. p. 224° (decomp.) (Found: C, 56·5; H, 6·2. $C_{24}H_{30}O_3NI$ requires C, 56·7; H, 5·9%).

Tropine phenyl-2-thienylglycollate was obtained by transesterification of tropine with ethyl phenyl-2-thienylglycollate, prepared from the silver salt of the free acid.[18] The acid-soluble product, crystallized from 70% (v/v) aqueous ethanol, had m. p. 151° (yield, 5%) (Found: C, 66·9; H, 6·0. $C_{20}H_{23}O_3NS$ requires C, 67·4; H, 6·4%).

Tropine 9-hydroxyfluorene-9-carboxylate was prepared by transesterification of tropine with ethyl 9-hydroxyfluorene-9-carboxylate; the product (8%), crystallized from 70% (v/v) aqueous ethanol, had m. p. 176° (Found: C, 75·7; H, 6·5. $C_{22}H_{23}O_3N$ requires C, 75·7; H, 6·6%). The *methiodide* was obtained as long needles (from ethanol), decomp. 190° (Found: C, 55·9; H, 5·4. $C_{23}H_{26}O_3NI$ requires C, 56·2; H, 5·3%).

DEPARTMENT OF PHARMACOLOGY, OXFORD. [*Received, April 10th*, 1957.]

[17] Bickel, *Ber.*, 1889, **22**, 1537.
[18] Blicke and Tsao, *J. Amer. Chem. Soc.*, 1944, **66**, 1645.

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709. *A New Solution of the Wave Equation for* H^-.

By B. F. GRAY and H. O. PRITCHARD.

A method of obtaining the exact solution of the wave equation for H^- from the known exact solution for H_2^+ is examined and shown to be satisfactory; the analysis shows that there exists only one state of the negative hydrogen ion which is stable with respect to a normal hydrogen atom.

INSPECTION of the wave equations for H^- and H_2^+, denoted in subscripts by A and B respectively, after separation of the translational motion, reveals that they are of the same form, differing only by an exchange of the masses of the electron and the proton, m and M respectively. If the lowest eigenvalue of the equation for H_2^+ is

$$E_B = E(M, m)$$

then it follows that

$$E_A = E(m, M)$$

with a similar relation holding for the eigenfunctions. This of course is only true for the exact eigenvalues and eigenfunctions, the difference $|E_A - \tilde{E}(m, M)|$ giving us a (very sensitive) test of the accuracy of an approximation $\tilde{E}(M, m)$ to E_B. This correspondence would, in principle, allow us to obtain E_B from E_A, but we cannot do this in practice because E_A has only been obtained directly by use of the variation principle.

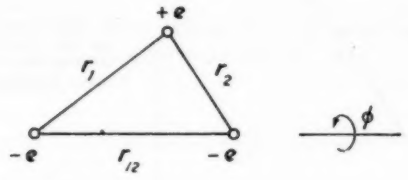
The wave equations of H^- and H_2^+ have not hitherto been identified purely because of

the choice of the origin of the co-ordinates. If for H^- we take a co-ordinate system (see Fig. 1) with

$$\xi = \frac{r_1 + r_2}{r_{12}}, \eta = \frac{r_1 - r_2}{r_{12}}, \text{ and } \phi$$

as our variables, then the wave equation is identical with that for H_2^+ with nuclear motion, except for the interchange of m and M. It is now permissible (the principle of covariance) to consider the electrons in H^- as moving in the field of a rapidly moving proton, *i.e.*, the " inverse " of the Born–Oppenheimer approximation for H_2^+. The reason is that the " electronic energy " of H_2^+ is an energy of motion of the electron *relative* to the two nuclei, and if this motion is rapid, it is equally permissible to speak of the motion of the two protons as rapid, relative to the electron. Whichever origin we choose, the energy of the relative motion must be invariant. Furthermore, it is convenient to separate off the energy of a hydrogen atom, corrected for nuclear motion; this energy is proportional to $[(1/m) + (1/M)]^{-1}$ and is clearly invariant under the mass transformation. Hence the bond dissociation energy of H_2^+ must transform into the ionisation potential of H^- and we can deal directly with these quantities.

FIG. 1.



Intuitively, the application of the principle of covariance means that we can picture the H^- ion as a proton about which is distributed a Morse-type oscillator, *i.e.*, the two electrons are vibrating with respect to each other and their motion relative to the nucleus is superimposed upon this vibration. They are, of course, also rotating relatively to an axis fixed in space, but the contribution to the effective potential from centrifugal effects is zero for the lowest energy level ($j = 0$) and is so great for $j = 1$ (owing to the small moment of inertia) that the system would ionise (the analogue of dissociation of molecules by rotation). Hence we need consider only the ground rotational levels of any electron vibrational states.

Curve A of Fig. 2 shows the total energy of H_2^+ (taken from the exact solution of the static wave equation by Bates, Ledsham, and Stewart [1]), referred to the (invariant) energy of a hydrogen atom as zero. This is now to be interpreted as representing the vibration with respect to each other of the two electrons in H^-. Assuming that this is a Morse curve, we can deduce the relevant constants (*i.e.*, D the minimum energy and a the anharmonicity constant) from a knowledge of three equally spaced points in the neighbourhood of the minimum.[2] The important quantity, which determines both the number of allowed energy levels and their energies,[3] is

$$k = [2\pi\sqrt{(M'D)}]/a\hbar$$

where M' is the mass of the vibrating particles (if they are both equal). For curve A we find that $k_2 = 20{\cdot}32$ whence $k_A = k_B/\sqrt{(1836)} \approx 0{\cdot}47$, and since for a Morse oscillator the number of allowed energy levels is the largest integer less than $(k + \frac{1}{2})$ this means that at

[1] Bates, Ledsham, and Stewart, *Phil. Trans.*, 1953, *A*, **246**, 215.
[2] Rosen, *Phys. Review*, 1931, **38**, 2099.
[3] Condon and Morse, " Quantum Mechanics," McGraw-Hill, New York, 1929, pp. 71—72.

this level of approximation H^- is not stable. (As a corollary, in the fixed-nucleus approximation, the equilibrium internuclear separation in H_2^+ is precisely $2a_0$, since this is the most probable interelectronic separation for this model of H^-.)

To obtain a positive electron affinity it is necessary to go to the next stage of approximation in H_2^+, *i.e.*, to include adiabatic coupling terms between the electronic and the nuclear motions. These have already been evaluated at some internuclear separations by Dalgarno and McCarroll [4] who found them to be repulsive below $2a_0$ but attractive at greater distances (but negligible at all separations, affecting only the fifth significant figure in the bond dissociation energy—this directly contradicted Wu and Bhatia [5] who found them to affect higher places, being repulsive for distances greater than $2a_0$). If we take Dalgarno and McCarroll's corrections which, although they are negligible for H_2^+ itself,

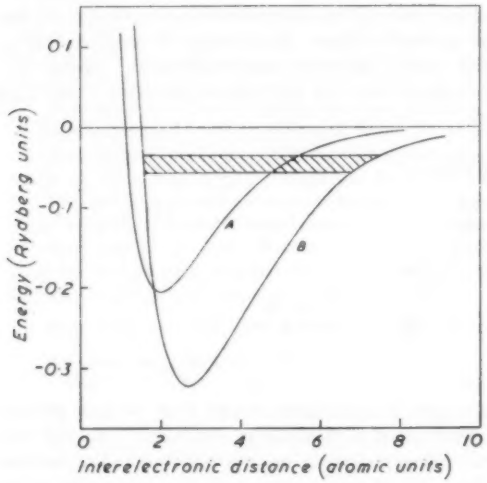


FIG. 2.

The shaded region represents the uncertainty in the zero-point energy arising from the assumption that curve B is a true Morse curve over the whole oscillation.

become multiplied by 1836 under the mass transformation, we obtain curve B of Fig. 2 for the variation of energy with interelectronic separation. This is a reasonable Morse curve, since fitting various sets of points gives values in the range $a = 1{\cdot}030 \pm 0{\cdot}065\, a_0^{-1}$ and $D = 0{\cdot}3290 \pm 0{\cdot}0075$ Rydberg. These mean values lead to a value for k_A of 0·788, thus establishing that there is almost certainly only one level of H^- stable with respect to a normal hydrogen atom (other states of H_2^+ lie very much higher in the energy spectrum although adiabatic coupling terms may be larger [4]). The energy of a Morse oscillator is

$$E = -D(k - n - \tfrac{1}{2})^2/k^2$$

where n, the quantum number of the vibration, can range from zero to the largest integer less than $(k - \frac{1}{2})$. Substituting the value of k found for curve B in this expression leads to an electron affinity of 0·044 Rydberg, *i.e.*, a total energy of $-1{\cdot}044 \pm 0{\cdot}012$ Rydberg, compared with the best variation calculation of $-1{\cdot}0554$ Rydberg.

In order to obtain the energy limit of the adiabatic approximation, it would be necessary to calculate the coupling corrections at more internuclear separations than are at present available [4] and to solve the wave equation numerically by using curve B for the potential energy, in order to avoid the assumption that it is a Morse curve. However, it is unlikely that the correct energy will be approached unless non-diagonal elements are considered in the coupling between nuclear and electronic motions. Nevertheless, we are dealing

[4] Dalgarno and McCarroll, *Proc. Roy. Soc.*, 1956, *A*, **237**, 383.
[5] Wu and Bhatia, *J. Chem. Phys.*, 1956, **24**, 48.

here with a process which converges to the correct eigenvalue (this has not yet been shown to be so for the Hylleraas method, particularly in the case of H^-); we hope to undertake this programme soon and at the same time to study the helium atom (*i.e.*, by solving the H_2^+ problem with a doubly-charged electron) for which there are many more stable levels, in order to establish the exact correspondence between the various states under the mass transformation, *i.e.*, the correspondence between electronic, vibrational, and rotational excitation for the molecule on the one hand, and electronic excitation and spin and orbital angular momentum for the atom on the other.

The energy value obtained in the present calculation proves beyond doubt that Dalgarno and McCarroll's corrections are correct; those of Wu and Bhatia would give an energy corresponding to an even more unstable system than is obtained without using the corrections. The calculation also re-emphasises the fact that it is only the total energy of the system which is meaningful and that the nature of the individual energy terms depends on how the problem is tackled. In our calculation, the individual terms are coulombic, kinetic, adiabatic coupling, and zero-point vibration energies, whereas in the standard treatments one has coulombic, kinetic, exchange, and correlation-energy terms; furthermore, the inclusion of coupling between nuclear and electronic motions increases the most probable interelectron distance from $2a_0$ to $2{\cdot}69a_0$, an effect which is associated with a " screening constant " in orbital treatments.

We thank Dr. A. Dalgarno and Dr. R. McCarroll for numerical values for the adiabatic coupling constants, and the D.S.I.R. for a grant (to B. F. G.).

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710. *A Proof of the Structure of Methyl β-D-Fructofuranoside prepared enzymically from Sucrose and Methanol.*

By J. S. D. BACON and D. J. BELL.

A substance prepared by the action of a yeast invertase preparation on sucrose in the presence of methanol has been shown by oxidation with periodate and preparation of derivatives to be methyl β-D-fructofuranoside. Some evidence is given supporting the view that it is formed by transfructosylation from sucrose to alcohol, catalysed by the invertase.

NELSON and SCHUBERT [1] found that addition of ethanol lowered the rate of hydrolysis of sucrose by yeast invertase, as measured by change in optical rotation; they attributed this to a decrease in the amount of available water. However, paper chromatography shows that in the presence of ethanol a new substance, probably ethyl β-D-fructofuranoside, is formed, and analogous products are obtained from a number of other alcohols.[2,3,4] Mould invertases behave in a similar manner.[5,6] There is evidence that homologous products are formed by the subsequent transfer of fructose residues to the simple fructosides.[5,7]

The substance formed in the presence of methanol was selected for closer examination, because the methyl fructosides have been studied by Purves and Hudson; they isolated

[1] Nelson and Schubert, *J. Amer. Chem. Soc.*, 1928, **50**, 2188.
[2] Bacon, *Biochem. J.*, 1952, **50**, xviii.
[3] Miwa, *Symposia on Enzyme Chemistry, Japan*, 1953, **8**, 57.
[4] Oparin and Bardinskaya, *Doklady Akad. Nauk S.S.S.R.*, 1953, **89**, 531.
[5] Bealing, *Biochem. J.*, 1953, **55**, 93.
[6] Kurasawa, Saito, Honma, and Yamamato, *Bull. Fac. Agric., Nigata Univ., Nigata, Japan*, 1955, **7**, 57.
[7] Breuer and Bacon, *Biochem. J.*, 1957, **66**, 462.

crystalline methyl α-fructofuranoside [8] and estimated the optical rotation of the β-anomer.[9]

Our product was at first separated by partition chromatography on cellulose powder, or by elution with water from charcoal–Celite,[2] but it was later found that a small gradient of ethanol in the water (0 ⟶ 10%) removed it from the charcoal after the monosaccharides, yet well in advance of the disaccharide fraction. In this way a single chromatographic separation yielded 5 g. from an incubation mixture containing initially 26 g. of sucrose.[7] The substance, which usually contained traces of fructose, was a syrup which has not yet crystallised. It was non-reducing, stable to alkali, but readily hydrolysed by dilute acid or by yeast invertase to yield fructose, and had the alkoxyl content (calculated as methoxyl) expected for a methyl hexoside. It reduced 1·01 moles of sodium metaperiodate per mole with the formation of less than 0·012 mole of acid. Subjected to Barry and Mitchell's phenylhydrazine–acetic acid degradation [10] the oxidised glycoside yielded only glycerosazone. Confirmation that the glycoside was indeed derived from D-fructose followed from its conversion [11] in high yield into 2 : 3-4 : 5-(" β ")-di-*O*-*iso*propylidene-D-fructopyranose.

These facts all agree with a fructofuranoside structure. The assignment of the β-configuration must perforce rest on the susceptibility of the substance to yeast invertase and on its negative rotation (cf. $[\alpha]_D^{20}$ +93° for methyl α-D-fructofuranoside).[8]

In 1939, Schlubach and Bartels [12] obtained the first authentic sample of methyl β-D-fructofuranoside, with $[\alpha]_D^{20}$ −49·95°, by a painstaking series of reactions starting with D-fructose 1 : 6-diphosphate, and concluding with enzymic dephosphorylation. If no ring enlargement occurred during the latter treatment, the structure of a furanoside must follow for their product; it was found, moreover, to be hydrolysed by invertase to the extent of 95%. More recently Augestad, Berner, and Weigner [13] have isolated the glycoside, by chromatography on cellulose powder, from the "γ-methyl fructoside" mixture; [14] their product (stated to be "97% pure" [15]) had $[\alpha]_D$ −46·9°.[13] Foster [16] has examined a sample of it ($[\alpha]_D$ −48°) by paper ionophoresis in the presence of sodium borate and finds it to have a mobility consistent with a β-fructofuranoside structure and quite different from that of the α-anomer, but as far as we know no chemical proof of its structure has yet been published. Purves and Hudson [9] calculated from the observed changes in reducing power and optical rotation when yeast invertase acted upon "γ-methyl fructoside" preparations that the $[\alpha]_D$ of methyl β-D-fructofuranoside should be −52° ± 2°. Our enzymically synthesised preparations had $[\alpha]_D$ between −50° and −52°. Similar independent preparations by Ishizawa and Miwa [17] had $[\alpha]_D$ −50·7°. If the figures for the enzymically synthesised products are taken as likely to be more nearly correct the agreement between them and the calculated value would seem to indicate that only one component of the γ-methyl fructoside mixture is attacked by yeast invertase preparations. (Wolfrom and Shafizadeh [18] have discussed the bearing of the figure of −46·9° on the accepted configuration of sucrose.)

For want of evidence to the contrary it has been assumed [19,20] that a single enzyme is responsible for both the fructose-transferring and the hydrolytic activity of yeast invertase preparations. If a sufficiently high concentration of methanol is chosen (5M), rather more fructoside than free fructose is formed during the breakdown of the first 20% of the sucrose.

[8] Purves and Hudson, *J. Amer. Chem. Soc.*, 1934, **56**, 708.
[9] *Idem*, *ibid.*, p. 702.
[10] Barry and Mitchell, *J.*, 1954, 4020.
[11] Bell, *J.*, 1947, 1461.
[12] Schlubach and Bartels, *Annalen*, 1939, **541**, 76; cf. Morgan and Robison, *Biochem. J.*, 1928, **22**, 1270.
[13] Augestad, Berner, and Weigner, *Chem. and Ind.*, 1953, 376.
[14] Menzies, *J.*, 1922, **121**, 2238.
[15] Augestad and Berner, *Acta Chem. Scand.*, 1954, **8**, 251.
[16] Foster, *J.*, 1957, 1395.
[17] Ishizawa and Miwa, *Symposia on Enzyme Chemistry, Japan*, 1954, **9**, 40.
[18] Wolfrom and Shafizadeh, *J. Org. Chem.*, 1956, **21**, 88.
[19] Bacon, *Ann. Reports*, 1954, **50**, 281.
[20] Edelman, *Adv. Enzymology*, 1956, **17**, 189.

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The ratio of these two quantities may then be measured conveniently by quantitative paper chromatography,[21] and serves as a measure of the ratio of transferring to hydrolytic activity (T/H). As would be expected, the ratio is influenced by the initial concentrations of methanol and sucrose, but when these were kept constant it was found to vary hardly at all over a wide range of pH (3·5—8·9), the greatest divergence being a decrease of about 20% at alkaline pH. (The latter effect did not appear to be due to epimerisation of glucose under the conditions of incubation and analysis.) The T/H ratios differed little for samples of enzyme taken at various stages of the autolysis of baker's yeast. It was slightly increased in this and other enzyme preparations by dialysis, which reduces the total enzymic activity considerably.[22]

A small amount of fructoside was shown chromatographically to be produced enzymically from mixtures of methanol and fructose, but this was insignificant compared with the magnitude of fructoside synthesis when sucrose was present. The evidence thus strongly suggests that methyl β-D-fructofuranoside is formed by the transfer of fructose residues from sucrose to methanol and that the enzyme responsible is that which causes the simultaneous hydrolysis of the sucrose.

We found the rate of hydrolysis of β-D-fructofuranoside by yeast invertase, relative to that of sucrose, to be somewhat faster than that recorded for the labile component of γ-methyl fructoside;[9] this discrepancy might be due to the inhibitory effects of the other components of the mixture. The fructoside can serve as a donor in transfructosylation reactions with both yeast [23] and mould [7] invertase.

Experimental

All aqueous solutions were evaporated under reduced pressure at pH 6—7, below 50°. Specific rotations were determined in water, a 2 dm. tube being used. Enzyme incubations were at 18—22° in the presence of chloroform, and were stopped by heating quickly to 100° or by the addition of mercuric chloride.

Factors influencing Fructoside Formation.—The rate of fructoside formation (concurrent with sucrose breakdown from 0 to 20%), under a variety of conditions, was followed by quantitative paper chromatography with a colorimetric method for ketose determination.[21] The free fructose liberated during the experiments was measured by the same method. The molar ratio, fructoside formed : fructose set free by hydrolysis, was calculated from these measurements; this ratio is termed T/H (" transfer/hydrolysis ").

(a) *Methanol concentration.* With 0·25M-sucrose at pH 5·0 fructoside formation was seen with methanol concentrations ranging from 1 to 40% (v/v); concentrations greater than 20% (~6M) eventually inactivated the enzyme. For the majority of measurements of T/H, 5M-methanol was chosen; at this concentration, and pH 5·0, in the absence of sucrose the enzyme lost about 10% of its activity in 20 hr. The majority of the incubations were stopped before this time; nevertheless some decrease in the rates of sucrose breakdown was noticed. With 10M-methanol, at the early stages of the reaction T/H was 2·7, compared with 1·45 when 5M-methanol was used; 10M-methanol was therefore used in the preparative work.[7]

(b) *Sucrose concentration.* T/H increased slightly with increasing sucrose concentration, namely from 1·3 at 0·125M to 1·8 at 0·5M. With 0·25M-sucrose, oligosaccharide formation (fructosyl transfer to sucrose [22]) accounted for only about 10% of the total transfructosylation.

(c) *Dependence on* pH. About 50 measurements of T/H were made with dialysed B.D.H. " Invertase Concentrate " acting on 0·25M-sucrose and 5M-methanol with acetate, barbiturate, and phosphate buffers to maintain the pH at values ranging from 3·5 to 8·9. In only three instances did T/H exceed 1·52 and in only one was it less than 1·13. These values were found over a range of sucrose-breakdown between 5 and 25%; over this range, at pH 5 T/H falls

[21] Bacon, in " Methods in Enzymology," Ed. Colowick and Kaplan, Academic Press, New York, 1955, Vol. I, p. 258.
[22] Bacon, *Biochem. J.*, 1954, **57**, 320.
[23] Whelan and Jones, *ibid.*, 1953, **54**, xxxiv.

slightly, from ~1·5 to ~1·4. A summary of the effect of pH at 17—23% sucrose-breakdown is given below; the fall in T/H at alkaline pH was noted in all experiments;

pH	3·6	4·6	5·0	5·6	6·3	7·0	8·0	9·0
T/H	1·39	1·40	1·46	1·44	1·44	1·52	1·23	1·25

That alkalinity alone had no effect on a mixture of fructose and glucose, in the absence of enzyme, was shown as follows. A solution of fructose (0·028M) and glucose (0·028M) in phosphate buffer (0·04M) at pH 9·0 was kept at 20°; samples were withdrawn at intervals, acidified with hydrochloric acid, and stored in the frozen state. Subsequent ketose measurements on the samples showed that no detectable change in the fructose content had occurred during 96 hr., a period which exceeded the duration of each of the enzyme experiments at alkaline pH.

Autolysis of Yeast.—A mixture of fresh baker's yeast (100 g.) with water (100 ml.) and toluene (40 ml.) was stirred intermittently and samples were removed at intervals. After centrifuging, the supernatant fluids were filtered by gravity in presence of Hyflo-Supercel and stored at 0° in presence of chloroform. Filtrates incubated at pH 5·0 with sucrose (0·25M) and methanol (0·5M) in acetate buffer (0·025M) gave the following results:

Time of removal of sample	Relative invertase activities	T/H
0	1	1·33
4 days	24	1·28
13 days	32	1·24

(Invertase activity was measured as release of reducing sugar, estimated by the method of Miller and Van Slyke.[24])

Effect of Dialysis on Invertase Preparations.—After dialysis against Sheffield tap-water for 20 hr. the 13-day autolysate had lost half of its original invertase activity and now gave T/H of 1·37. A sample of B.D.H. "Invertase Concentrate" which had lost 95% of its activity on dialysis against tap water, gave T/H 1·51 against 1·35 for the undialysed preparation (12% sucrose-breakdown). The latter was examined at a dilution of 1 : 2500 (v/v) so that the fructosyl-accepting effect of the glycerol which it contained might be expected to be negligible; this was confirmed by the addition to the incubation mixture with the dialysed B.D.H. invertase, of glycerol at 1% and 10% (v/v) levels, when T/H ratios of 1·51 and 1·50 respectively were found. Two different undialysed B.D.H. preparations gave indistinguishable T/H over the range 5—17% sucrose-breakdown, 1·38 and 1·42 at 5%; 1·31 and 1·31 at 17%.

Fructoside Formation from Free Fructose and Methanol.—Enzymic incubation of fructose (0·7M) with methanol (10M) at pH 6 yielded less than 1 mg./ml. of material showing the chromatographic behaviour of methyl β-fructofuranoside. A T/H ratio of 2·7 at 20% sucrose-breakdown corresponds to 13 mg./ml. of the glycoside being formed. When the action of the enzyme on sucrose–methanol systems was continued for 10—100 times the duration needed for complete breakdown of the sucrose the fructoside level fell to that formed in the free fructose–methanol system.

Isolation of the Fructoside.—The analytical methods used, and a typical procedure for the isolation of the fructoside, have already been described.[2, 7] The substance had an R_F of 0·37—0·40 in butanol–acetic acid;[25] Miwa found R_F 0·40 for his product.[26]

125 mg. of a preparation purified by chromatography on cellulose powder and charcoal–Celite columns and containing no detectable monosaccharide were dissolved in 3·0 ml. of water. The solution had a rotation of −3·93° (at 22°), and estimations of ketose, and of reducing sugar after hydrolysis with 0·5% oxalic acid at 100° for 30 min., showed 36·2 and 36·5 mg./ml. respectively, corresponding to $[\alpha]_D^{22}$ −50·4° and −49·9°. Paper chromatograms of the hydrolysate showed a single spot, corresponding to fructose (Found : OMe, 16·0. Calc. for $C_7H_{14}O_6$: OMe, 16·0%).

Characterisation of the Fructoside.—(a) *Products of periodate oxidation.* After drying to constant weight over phosphoric oxide at 15 mm., the glycoside (0·7205 g., 3·714 millimoles) was dissolved in water (20 ml.), and 0·3M-sodium metaperiodate solution (25 ml.) added. A control with water and periodate was set up at the same time. Samples of both solutions were

[24] Miller and Van Slyke, *J. Biol. Chem.*, 1936, **114**, 583.
[25] Partridge, *Biochem. J.*, 1948, **42**, 238.
[26] Miwa, personal communication.

titrated with 0·05N-sodium arsenite solution in the usual way. At 17 hr. the glycoside (1·00 mol.) reduced 1·01 mols. of IO_4^-; at 24 hr., 1·00 mol. Titration of the solution with 0·01N-potassium hydroxide, after destruction of periodate by purified ethylene glycol, showed that less than 0·012 mol. of acid had been formed.

Treated with phenylhydrazine and dilute acetic acid according to Barry and Mitchell [10] with addition of 0·2 ml. of saturated potassium metabisulphite solution to the reaction medium,[27] the oxidation product (from 485 mg. of glycoside) yielded 370 mg. of glycerosazone (stout needles from benzene), m. p. and mixed m. p. 131—132°. Chromatography [10] both by column and paper gave no evidence of the presence of glyoxalosazone or of higher osazones among the products of this reaction. A repetition of the whole experiment gave similar results.

(b) *Treatment with acetone–5% sulphuric acid.*[11] The glycoside (580 mg.) was shaken with 30 ml. of dry ($CaSO_4$) acetone containing 1 ml. of sulphuric acid. Dissolution was complete in 30 min. After 6 hr. at room temperature the product was isolated as a hard crystalline mass (715 mg., 92%), m. p. 95—96°. Recrystallised from ligroin (b. p. 60—80°), needles (620 mg.) were obtained with m. p. and mixed m. p. 95—96°, $[\alpha]_D^{18}$ −24·8°.[11]

Hydrolysis of the Fructoside by Yeast Invertase.—The action of undialysed Invertase Concentrate on 0·12M-methyl β-fructoside, and on 0·13M-sucrose at pH 5·0 was compared. On the assumption that fructose is half of the total reducing sugar liberated from sucrose, the mg. of fructose liberated per ml.[24] were:

Time (min.)	15	30	60	90	120	180	300
Sucrose	4·40 *	8·55	14·9	—	—	—	—
Fructoside	—	1·25	2·47	3·05	3·95*	5·87	10·0

From the figures marked (*) the ratio of the rates of breakdown (on a molar basis) may be calculated as 8·7 : 1. Purves and Hudson [9] found a value of 13·5 : 1 in their experiments with γ-methyl fructoside mixtures.

Comparison with γ-Methyl Fructoside Mixture.—Preparations of γ-methyl fructoside [9] showed, in addition to fructose, two faster-running spots on butanol–acetic acid chromatograms (R_F 0·39, 0·46). Both disappeared when the preparation was treated with 0·5% oxalic acid at 100° for 30 min. Yeast invertase was observed qualitatively to act upon that with R_F 0·39, *i.e.*, the one corresponding to methyl β-fructofuranoside. However, prolonged incubation under conditions in which the enzyme was proved to retain its activity failed to cause the complete disappearance of the spot (in the presence of a final concentration of about 0·2M-fructose). No change could be seen in the other spot during the enzyme treatment. Chromatograms of sucrose or of fructose which had been treated with 0·5% oxalic acid at 100° in the presence of 25% methanol showed two spots with R_F 0·39 and 0·45. The amounts of these substances were small; they were comparable with the yield of methyl β-fructofuranoside from enzyme action on mixtures of fructose and methanol.

We thank Mrs. B. Sutton for carrying out most of the experiments with yeast invertase. We are also grateful to Dr. T. Miwa for details of his work, not yet published in English, and to Drs. V. C. Barry and P. W. D. Mitchell for the gift of osazones.

THE DEPARTMENTS OF BIOCHEMISTRY,
UNIVERSITIES OF SHEFFIELD AND CAMBRIDGE.
[Present Addresses:
(J. S. D. B.) MACAULAY INSTITUTE, CRAIGIEBUCKLER, ABERDEEN.
(D. J. B.) A.R.C. POULTRY RESEARCH CENTRE,
EDINBURGH, 9.]

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[27] Hamilton, *J. Amer. Chem. Soc.*, 1934, **56**, 487.

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711. *The Relative and Absolute Configurations of Catechins and* epi*Catechins.*

By A. J. Birch, J. W. Clark-Lewis, and A. V. Robertson.

The 3-hydroxyl groups in (+)-catechin and (−)-*epi*catechin 5 : 7 : 3′ : 4′-tetramethyl ether are of opposite configuration as reductive ring-opening and methylation gave enantiomorphous pentamethoxy-1 : 3-diarylpropan-2-ols. Epimerisation of catechins and *epi*catechins therefore results from inversion of the 2-aryl and not of the 3-hydroxyl group.[1] Prelog's atrolactic acid method[2] has been used to determine the absolute configurations of the catechins and *epi*catechins, the first of such determinations with flavan derivatives. Hydroxyl stretching frequencies of (+)-catechin and (−)-*epi*catechin tetramethyl ethers indicate strong intramolecular hydrogen bonding of 3(a)-hydroxyl groups and hence the existence of these compounds in the preferred 2(a)aryl : 3(a)hydroxyl and 2(e)aryl : 3(a)hydroxyl conformations respectively.

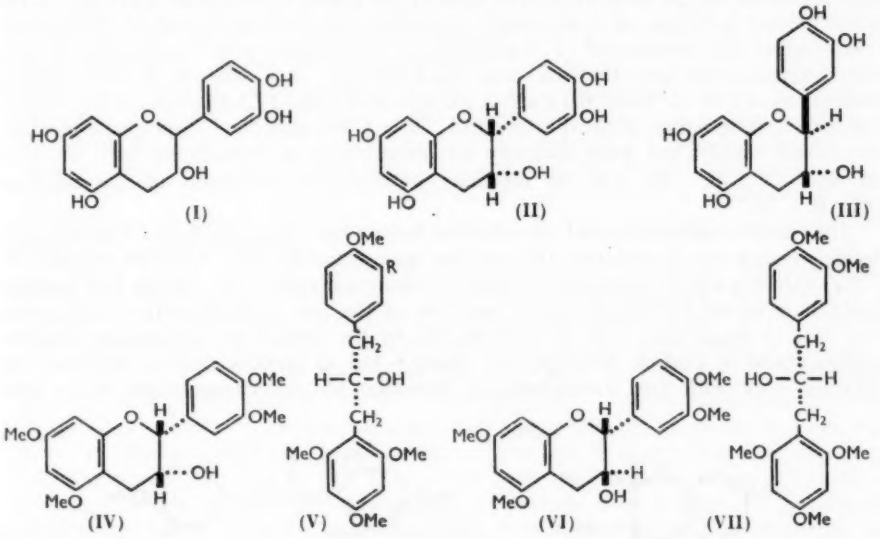
Catechin and *epi*catechin were shown to be 5 : 7 : 3′ : 4′-tetrahydroxyflavan-3-ols (I) in classical structural studies by Freudenberg and his school,[3] completed in 1925[4] and reviewed by Mason.[5] Although the nature of the geometrical isomerism in these diastereoisomers was clear, it was not then possible to decide whether catechin or *epi*catechin is the *cis*-compound (II), and evidence cited by Freudenberg[6] was later regarded as equivocal,[7] so that the question remained undecided.[8] Interpretation of Freudenberg's data in terms of modern stereochemical theory, however, establishes *epi*catechin as the *cis*- (II) and catechin as the *trans*-isomer (III), and reasons for these assignments were recently discussed in detail by King, Clark-Lewis, and Forbes,[9] and by Whalley.[10] Outstanding features of catechin stereochemistry, and particularly the relative and absolute configurations, have now been elucidated and are discussed below.

Epimerisation and racemisation of catechins occurs in hot aqueous solutions under a variety of conditions,[11, 12] and the resulting interconversions have been summarised by Freudenberg and Purrmann.[12] (+)-Catechin is thus partially converted into (+)-*epi*catechin, and similarly (−)-*epi*catechin yields some (−)-catechin; these transformations clearly result from inversion at one only of the two asymmetric centres. Freudenberg[3, 13] assumed that epimerisation occurred by inversion of the 2-aryl group (*viz.*, II ⟶ III, and III ⟶ II) and we have proved this assumption correct.

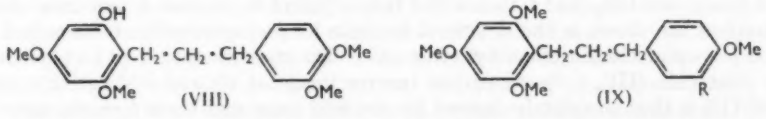
This was carried out by removing the asymmetry of the centre carrying the 2-aryl group. The C–O bond at this centre is of the benzyl ether type, and bonds of this type are usually smoothly reduced by sodium and ethanol in liquid ammonia, provided the rings do

[1] Birch, Robertson, and Clark-Lewis, *Chem. and Ind.*, 1956, 664.
[2] Prelog, *Helv. Chim. Acta*, 1953, **36**, 308; Prelog and Meier, *ibid.*, p. 320; Dauben, Dickel, Jeger, and Prelog, *ibid.*, p. 325; cf. "Progress in Stereochemistry," Butterworth, London, 1954, Vol. I, p. 198.
[3] Freudenberg, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 153.
[4] Freudenberg, Fikentscher, Harder, and Schmidt, *Annalen*, 1925, **444**, 135; for earlier work see refs. 3 and 5.
[5] Mason, *J. Soc. Chem. Ind.*, 1928, **47**, 269.
[6] Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 157; Freudenberg, Fikentscher, and Wenner, *ibid.*, **442**, 309; Freudenberg, Carrara, and Cohn, *ibid.*, 1926, **446**, 87.
[7] Freudenberg and Harder, *Annalen*, 1927, **451**, 213 (see footnote 3, p. 214); Hückel, Neunhoeffer, Gercke, and Frank, *ibid.*, 1930, **477**, 99 (see p. 159).
[8] Freudenberg and Harder, ref. 7; Freudenberg, Cox, and Braun, *J. Amer. Chem. Soc.*, 1932, **54**, 1913; Freudenberg and Oehler, *Annalen*, 1930, **483**, footnote, p. 141.
[9] King, Clark-Lewis, and Forbes, *J.*, 1955, 2949.
[10] Whalley, "The Stereochemistry of the Chromans and Related Compounds," Symposium on Vegetable Tannins, Cambridge, April, 1956, Society of Leather Trades' Chemists, Croydon, 1956, p. 151.
[11] Freudenberg, Böhme, and Purrmann, *Ber.*, 1922, **55**, 1734; Freudenberg and Purrmann, *Ber.*, 1923, **56**, 1185.
[12] Freudenberg and Purrmann, *Annalen*, 1924, **437**, 274.
[13] Freudenberg and Oehler, *ibid.*, 1930, **483**, 140.

not carry free phenolic groups.[13a] (−)-*epi*Catechin tetramethyl ether (IV) was so reduced, and methylation of the resulting phenolic alcohol gave 1-(3 : 4-dimethoxyphenyl)-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol with an excess of the (+)-enantiomorph * (V; R = OMe) (lævorotatory in EtOH, dextrorotatory in $CHCl_3$). Similar reduction of (+)-catechin tetramethyl ether (VI) and methylation gave the propan-2-ol with an excess of the (−)-enantiomorph * (VII) (dextrorotatory in EtOH, lævorotatory in $CHCl_3$). We infer that (+)-catechin and (−)-*epi*catechin tetramethyl ethers (and hence also the free phenols) have opposite configurations at position 3 so that (+)-catechin and (+)-*epi*catechin have the same configuration at this position, and therefore epimerisations of (+)-catechin to (+)-*epi*catechin and of (−)-*epi*catechin to (−)-catechin occur by inversion of the 2-aryl group. Conditions for reduction to the optically active propanols appear to be critical



and, for reasons which are not yet completely clear (see below), some reductions of the (+)-catechin compound (VI) gave only racemic propanol. Reduction to the phenolic alcohol was accompanied in each case by formation of the related propane (VIII), and after methylation the propanol (VII or V; R = OMe) was separated from the 1 : 3-diarylpropane (IX; R = OMe) by chromatography. The phenolic propane (VIII) had earlier been obtained by reduction of catechin [14] and *epi*catechin tetramethyl ethers [14b] with sodium and alcohol; its methyl ether (IX; R = OMe),[14] synthesised by Freudenberg,[15] was a key compound in structural investigations of the catechins.[5]



(−)-*epi*Afzelechin trimethyl ether [9] (X), which has the same configuration as (−)-*epi*-catechin tetramethyl ether (IV), was similarly reduced with sodium in liquid ammonia, and

* Prefixes (+) and (−) refer to the direction of rotation of the propanols in aprotic solvents.

[13a] Birch, Hughes, and E. Smith, *Austral. J. Chem.*, 1955, **7**, 83; Birch, E. Smith, and Speake, unpublished work.

[14] (*a*) Kostanecki and Lampe, *Ber.*, 1907, **40**, 720; (*b*) Freudenberg and Cohn, *Ber.*, 1923, **56**, 2127.

[15] Freudenberg, *Ber.*, 1920, **53**, 1416.

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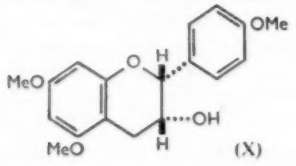
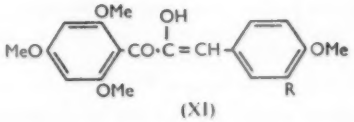
methylation of the phenolic products gave a mixture, separable by crystallisation, of the diarylpropane (IX; R = H) and diarylpropanol containing an excess of the (−)-enantiomorph (V; R = H) (lævorotatory in EtOH, $C_2H_2Cl_4$, and $CHCl_3$). As (−)-*epi*catechin tetramethyl ether (IV) gave the (+)-propanol (V; R = OMe) (dextrorotatory in $CHCl_3$ and $C_2H_2Cl_4$, lævorotatory in EtOH) it is now evident that the (−)-propanols (V; R = H) and (VII) have opposite configurations. Tacit assumption of the converse led us to incorrect conclusions [1] regarding the relative configurations of the catechins. It seems evident that no conclusions can be drawn in the diarylpropanol series by comparisons of the signs of rotation of different compounds at the D-line: rotational dispersion spectra may be more informative.*

The structures of the three optically active propanols (VII and V; R = OMe or H) were confirmed by the identity in each case of the infrared absorption spectrum of the active alcohol with that of its racemate synthesised from the appropriate 1 : 2-diketone. Condensation of ω-acetoxy-2 : 4 : 6-trimethoxyacetophenone with veratraldehyde and with *p*-anisaldehyde gave the two enolic diketones (XI; R = OMe or H) with infrared absorptions at 2·95—2·96 and 6·0 μ which are typical of enolic 1 : 2-diketones of this type.[16] Catalytic hydrogenation of the diketone (XI; R = OMe) gave the (±)-propan-2-ol which crystallised readily, but great difficulty was experienced in crystallising both the (−)-propanol (V; R = H) and its racemate obtained by reduction of the diketone (XI; R = H).

The relative configurations of the catechins having been thus established it remained to decide whether the *cis*-structure (II) and the *trans*-structure (III) represent respectively (−)-*epi*catechin and (−)-catechin, or their (+)-enantiomorphs. In principle this question might be resolved by examination of any one of the four optically active compounds, (+)- or (−)-*epi*catechin, (+)- or (−)-catechin, by the method for determining absolute configurations of alcohols developed by Prelog,[2] but in practice decisive evidence was obtained only with the *cis*-compounds. Reaction of methylmagnesium iodide with



(X)



(XI)

(−)-*epi*catechin tetramethyl ether 3-phenylglyoxylate and hydrolysis of the ester gave atrolactic acid with $[\alpha]_D$ −16·4° (after three crystallisations) equivalent to a 43% excess of the (−)-isomer. The atrolactic acid obtained similarly from (−)-*epi*afzelechin 5 : 7 : 4′-trimethyl ether had $[\alpha]_D$ −30·4° (after three crystallisations) corresponding to an 81% excess of the (−)-isomer, thus confirming the steric identity of the *epi*afzelechin and *epi*catechin compounds already inferred.[9] Formation of (−)-atrolactic acid in these reactions indicates that the Fischer projection for the (−)-*epi*-compounds is (A), in which M is the group with CH_2, and L that with CHAr adjacent to position 3, and these absolute configurations are shown in the structural formulæ for (−)-*epi*catechin tetramethyl ether (IV) and (−)-*epi*afzelechin trimethyl ether (X). The stereochemistry of (−)-*epi*catechin (II), (−)-catechin (III), (+)-*epi*catechin (mirror image of II) and (+)-catechin (mirror image of III) is thus completely defined for the first time, and these formulæ agree with Freudenberg's recent conjecture.[3]

* Through the kindness of Dr. C. Djerassi (Wayne University) these have been examined. The curves for the alcohols from (−)-*epi*catechin tetramethyl ether and (−)-*epi*afzelechin trimethyl ether (in MeOH) are closely similar in shape and attain high positive values in the region of 300 mμ; the curve for the alcohol from (+)-catechin tetramethyl ether is enantiomeric. This result confirms the present conclusions on the identical configurations of the first two substances.

[16] Barnes and Pinkney, *J. Amer. Chem. Soc.*, 1953, **75**, 479.

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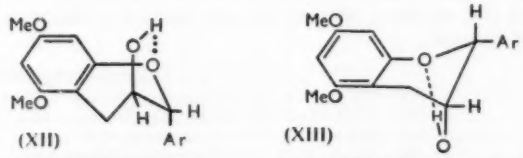
(+)-Catechin tetramethyl ether (VI; Fischer projection B) was expected to yield the (+)-acid when examined by Prelog's method, but hydrolysis of the 3-atrolactate gave atrolactic acid with $[\alpha]_D$ −1·1° corresponding to a 3% excess of (−)-acid. The experiment was repeated with similar results and it was proved that the lævorotation of the acid was

not caused by incomplete hydrolysis of the ester, by glycol formation,[17] or by contamination with lævorotatory (+)-catechin tetramethyl ether. In 3β-cholestanol phenylglyoxylate the ester group is flanked by two methylene groups and gave atrolactic acid with low optical activity, so that stereochemical inferences were considered inadvisable.[17] In the present case steric hindrance to reaction at the phenylglyoxylate carbonyl group due to the 2-aryl substituent is clearly much less in the *trans*- (catechin) than in the *cis*-series (*epi*-catechin), particularly in the diaxial *trans*-conformation where the proximate atoms are the 2(e)H and 4(quasi e)H. A low degree of asymmetric synthesis is therefore to be expected from (+)-catechin tetramethyl ether 3-phenylglyoxylate, and moreover from examination of models it seems to us plausible that slightly less hindrance should be offered from the side of the 2- than of the 4-position, which would account for the formation of (−)-atrolactic acid.

Several recent communications [18-20, 10] have dealt with possible conformations of flavan-3-ols, and a detailed analysis of the problem led Whalley [10] to conclude that the preferred conformations for catechins and *epi*catechins are probably those with 2(a)-aryl : 3(a)hydroxyl and 2(e)aryl : 3(a)hydroxyl arrangements of substituents respectively. The first decisive evidence supporting this conclusion is provided by the infrared absorptions of the hydroxyl groups of (+)-catechin and (−)-*epi*catechin tetramethyl ethers in carbon tetrachloride solution, measured and interpreted by Dr. A. R. H. Cole, which occur at 3594 and 3587 cm.$^{-1}$ respectively. These low hydroxyl stretching frequencies and the absence of a free hydroxyl band near 3630 cm.$^{-1}$ indicate strong intramolecular hydrogen bonding of axial hydroxyl groups, as postulated by Roberts.[18] (+)-Catechin tetramethyl ether (VI) and (−)-*epi*catechin tetramethyl ether (IV) therefore exist



in the preferred conformations (XII and XIII; Ar = 3 : 4-dimethoxyphenyl). Weaker hydrogen bonding in the catechin compound (XII), indicated by the higher hydroxyl stretching frequency, is attributed to a tendency for conformational inversion.[21] Intramolecular hydrogen bonding of this type was first proposed in connection with R_F values by Roberts,[18] whose further conclusions however required modification.[10, 19, 20] The higher R_F value of catechin compared with that of *epi*catechin suggests that the former molecule is less compact; this may indicate [10, 19, 20] that catechin itself exists in the same

[17] Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325.
[18] Roberts, *Chem. and Ind.*, 1955, 631, 1551.
[19] Clark-Lewis, *ibid.*, p. 1218.
[20] Roberts, *ibid.*, 1956, 737.
[21] Kuhn, *J. Amer. Chem. Soc.*, 1954, **76**, 4323; Cole and Jefferies, *J.*, 1956, 4391.

conformation as its methyl ether (XII; Ar = 3 : 4-dimethoxyphenyl). A similar argument applies to gallocatechin which has a higher R_F value than *epi*gallocatechin.

The conclusions reached here concerning the relative and absolute configurations of catechins and *epi*catechins may be taken to apply generally to other members of this class of compound,[9,22] for example, to (−)-*epi*afzelechin, (+)-gallocatechin, and (−)-*epi*-gallocatechin, and to their stereoisomers which await discovery. The interesting uniformity [9] of the occurrence of these natural products in the forms (+)-catechin, (+)-gallocatechin, (−)-*epi*afzelechin, (−)-*epi*catechin, and (−)-*epi*gallocatechin is now seen to reside in the identity of their configurations at the 2-position, and all these compounds may be defined as (2*R*)-flavan derivatives according to the method for specification of absolute configuration proposed by Cahn, Ingold, and Prelog.[23] The sign of rotation, however, is (+) or (−) according to the configuration (3*S* or 3*R* respectively) of the 3-hydroxyl group (Table). The configurational prefixes *D* and *L* decided by the position of the hydroxyl group in the Fischer projections (A) and (B) have little significance when applied to catechins,[3,24] although it can be seen that (3*S*) corresponds to *L*-, and (3*R*) corresponds to *D*-configurations in Fischer projection formulæ written with the higher-numbered asymmetric carbon atom at the bottom. This fortuitous correspondence resulting from the arbitrary conventions involved (*e.g.*, for numbering) does not imply a relationship with the D- or L-series of amino-acids and carbohydrates, which can, however, be determined by comparison of the respective absolute configurations.

The reductions recorded above present some aspects of general interest. The formation of the propanes is unlikely to be due to direct hydrogenolysis since the hydroxyl groups are not in benzyl positions. It may be due to an alkali-catalysed elimination of a molecule of water, to produce the propene, and subsequent reduction of this made possible by conjugation of the double bond with a benzene ring. Alternatively, an elimination could occur *during* the reduction when an anionic charge is formed in the 2-position and could transfer to the hydroxyl group with formation of a conjugated double bond. The extent of the reaction would probably be related to the length of existence of the anion. The formation in some cases of optically inactive propanol may result from an alkali-catalysed opening of the heterocyclic ring to produce initially the propanone, which is then further reduced to the (±)-propanol. Similar ring-openings have been observed.[25] The variations in results are therefore probably related to details of the experimental work, in particular the presence or absence of ethanol, the speed with which the reduction is carried out, and the efficiency of the stirring. Strongly alkaline conditions and slow reactions are to be avoided.

Compound	Structure and absolute configuration
(+)-Catechin	(2*R* : 3*S*)-5 : 7 : 3′ : 4′-Tetrahydroxyflavan-3-ol
(+)-Gallocatechin	(2*R* : 3*S*)-5 : 7 : 3′ : 4′ : 5′-Pentahydroxyflavan-3-ol
(−)-*epi*Afzelechin	(2*R* : 3*R*)-5 : 7 : 4′-Trihydroxyflavan-3-ol
(−)-*epi*Catechin (II)	(2*R* : 3*R*)-5 : 7 : 3′ : 4′-Tetrahydroxyflavan-3-ol
(−)-*epi*Gallocatechin	(2*R* : 3*R*)-5 : 7 : 3′ : 4′ : 5′-Pentahydroxyflavan-3-ol
(+)-Propanol (V; R = OMe)	(2*S*)-1-(3 : 4-Dimethoxyphenyl)-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol
(−)-Propanol (VII)	(2*R*)-1-(3 : 4)Dimethoxyphenyl)-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol
(−)-Propanol (V; R = H)	(2*S*)-1-*p*-Methoxyphenyl-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol

Experimental

Infrared measurements, except where otherwise noted, were made with a Grubb-Parsons S4 spectrometer equipped with a sodium chloride prism.

(−)-epi*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (IV).—Methylation of (−)-*epi*catechin, $[\alpha]_D^{17}$ −60° (2% in EtOH) (lit.,[12] $[\alpha]_{578}$ −68·2°), with dimethyl sulphate and potassium carbonate in acetone gave the tetramethyl ether, m. p. 136—139°, $[\alpha]_D^{17}$ −55° (4% in $C_2H_2Cl_4$) (lit.,[12] m. p.

[22] Schmidt and Mayer, *Angew. Chem.*, 1956, **68**, 103.
[23] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[24] Compare discussion of camphor by Freudenberg and Lwowski, *Annalen*, 1955, **594**, 76.
[25] Birch and D. C. C. Smith, unpublished work.

153—154°, $[\alpha]_{578}$ −61·5°) (Found: C, 65·9; H, 6·4. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%). Paper chromatograms (Bu^nOH–AcOH–H_2O) showed that the (−)-*epi*catechin (R_F 0·63) was free from (+)-catechin (R_F 0·75 on the same chromatogram); it presumably contained (±)-*epi*catechin (11%). The hydroxyl absorption of the tetramethyl ether occurred at 3587 cm.$^{-1}$; a 1 cm. layer of a dilute solution in carbon tetrachloride (*ca.* 1·7 mg./c.c.) was used, and measurements were made with a Grubb-Parsons S3A spectrometer equipped with a calcium fluoride prism.

(+)-*Catechin* 5 : 7 : 3′ : 4′-*tetramethyl ether* (VI), m. p. 143—144°, $[\alpha]_D^{20}$ −13·4° (10% in $C_2H_2Cl_4$) (lit.,[12] m. p. 143—144°, $[\alpha]_{578}$ −13·4°), was similarly prepared by methylation of (+)-catechin (Found: C, 65·9; H, 6·4%). Hydroxyl absorption occurred at 3594 cm.$^{-1}$ when examined under the same conditions as for the *epi*catechin analogue.

Reduction of (−)-epi*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (IV) *by Sodium and Liquid Ammonia.*—Sodium (0·3 g., 2·2 equiv.) in small pieces was added to (−)-*epi*catechin tetramethyl ether (2·1 g.) in ethanol (25 c.c.) and liquid ammonia (400 c.c.). The solution was evaporated on a warm water-bath after the addition of ammonium chloride (2 g.), and the semisolid residue was treated with water (50 c.c.) and 2N-hydrochloric acid (10 c.c.) before extraction with chloroform. Removal of the chloroform left a gum (2·2 g.) which was dissolved in benzene (10 c.c.) and extracted with dilute aqueous sodium hydroxide (10 × 10 c.c.) to remove phenols completely, and evaporation of the benzene then gave *epi*catechin tetramethyl ether (0·65 g., 31% recovery), of m. p. 137—140° and $[\alpha]_D^{18}$ −54° (8% in $C_2H_2Cl_4$) after crystallisation from methanol. The alkaline extract (100 c.c.) was shaken for 1 hr. at room temperature with dimethyl sulphate (2 c.c.), and the excess of dimethyl sulphate was destroyed with aqueous ammonia before extraction of the solid product (1·4 g.) into ether. This material was separated by chromatography on acid-washed alumina into the 1 : 3-diarylpropane (IX; R = OMe) (0·38 g., 18%), which was eluted by benzene and crystallised from ethanol in needles, m. p. 88—89° (lit.,[15, 26] m. p. 87—88°) (Found: C, 69·5; H, 7·6. Calc. for $C_{20}H_{26}O_5$: C, 69·3; H, 7·6%), and a gum (1·0 g.) which was eluted by benzene containing chloroform (10%) and when kept gave crystalline 1-(3 : 4-*dimethoxyphenyl*)-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-ol (V; R = OMe) (0·25 g., 12%). Recrystallisation from *cyclo*hexane containing benzene (10%) or ethanol (10%) gave prisms, m. p. 87—88°, $[\alpha]_D^{18}$ +1·0° (8% in $CHCl_3$), $[\alpha]_D^{18}$ +0·6° (10% in $C_2H_2Cl_4$), $[\alpha]_D^{20}$ −1·7° (10% in EtOH) (Found: C, 66·3; H, 7·3; OMe, 41·7. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2; 5OMe, 40·1%). The infrared absorption spectrum of the active propanol in CCl_4 was identical with that of the (±)-propanol described below.

Reductions of (+)-*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (VI) *by Sodium and Liquid Ammonia.*—(*a*) Reduction of the catechin compound (2·1 g.) as described above for the *epi*catechin isomer gave recovered catechin tetramethyl ether (1·1 g., 52%), m. p. 143—144°, $[\alpha]_D^{24}$ −13·4°, the 1 : 3-diarylpropane (IX; R = OMe) (0·25 g., 12%), and a benzene–chloroform eluate (0·39 g., 18%) from which the diarylpropanol (VII) (0·17 g., 8%) separated. After recrystallisation the *propanol* had m. p. 87—88°, $[\alpha]_D^{21}$ −2·5° (4% in $CHCl_3$) (Found: C, 66·1; H, 7·3%). The reduction was repeated and gave the propanol (VII), $[\alpha]_D^{25}$ +1·0° (4% in EtOH). The infrared absorption spectrum of the propanol in CCl_4 was indistinguishable from that of the enantiomorph or that of the synthetic (±)-propanol described below.

(*b*) Reduction of (+)-catechin tetramethyl ether (2·8 g.) with sodium (0·8 g., 4 equiv.), in an attempt to increase the yield of propanol, gave no recovered catechin but gave the propane (IX; R = OMe) (1·84 g., 66%) and the propanol (VII), which eventually crystallised (0·29 g., 10%) and after recrystallisation had no observable rotation (6% in $CHCl_3$, and 4% in $C_2H_2Cl_4$). Reduction under these conditions was repeated and the phenolic fraction, isolated in this instance before methylation, partially crystallised. Recrystallisation of this phenol from *cyclo*hexane–ethanol (10%) gave 1-(3 : 4-dimethoxyphenyl)-3-(2-hydroxy-4 : 6-dimethoxyphenyl)-propane (VIII) in prisms, m. p. 94—95° (lit.,[14b] m. p. 89—90°) (from carbon tetrachloride) (Found: C, 68·5; H, 7·4. Calc. for $C_{19}H_{24}O_5$: C, 68·6; H, 7·3%), which was converted by methylation into the propane (IX; R = OMe), m. p. and mixed m. p. 88—89°.

(*c*) Catechin tetramethyl ether (1·05 g.) was reduced with sodium (0·15 g., 2 equiv.) as described for the *epi*catechin compound except that ethanol was omitted. No catechin tetramethyl ether was recovered and, after methylation of the phenolic product (*ca.* 80%), the propane (IX; R = OMe) (0·19 g., 18%) and the propanol (VII) (0·25 g., 23%) were isolated. The recrystallised propanol was optically inactive (7% in $CHCl_3$).

[26] Drumm, O'Reilly, and Ryan, *Proc. Roy. Irish Acad.*, 1925, **37**, *B*, 19.

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Reduction of (−)-epi*Afzelechin* 5 : 7 : 4′-*Trimethyl Ether* (X) *by Sodium and Liquid Ammonia.* —(*a*) (−)-*epi*Afzelechin 5 : 7 : 4′-trimethyl ether [9] (1·8 g.), m. p. 112—113°, $[\alpha]_D^{24}$ −63° (2% in EtOH), was treated with sodium (0·46 g.) and liquid ammonia as described above for the catechin compound (method *b*). The phenolic products failed to crystallise but, after methylation with dimethyl sulphate, fractional crystallisation gave 1-p-*methoxyphenyl*-3-(2 : 4 : 6-*trimethoxyphenyl*)*propane* (IX; R = H) (0·36 g., 20%), needles, m. p. 67—68° (from ethanol) (Found: C, 71·8; H, 7·6. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·6%), as the fraction more soluble in light petroleum, and 1-p-*methoxyphenyl*-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-*ol* (V; R = H) (0·28 g., 15%) which was more soluble in ethanol and crystallised from light petroleum in needles, m. p. 77—78°, $[\alpha]_D^{24}$ −3·2° (18% in $C_2H_2Cl_4$) (Found: C, 68·6; H, 7·3. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·3%). Similarly (−)-*epi*afzelechin trimethyl ether (1·2 g.) was reduced with sodium (0·36 g., 4 g.-atoms/mole) and gave the propane (0·5 g., 42%), eluted from alumina with 7 : 3 benzene–light petroleum (b. p. 60—80°), and the crude propanol (0·35 g., 28%) eluted with 95 : 5 benzene–chloroform. After five crystallisations from light petroleum (b. p. 67—70°), the propanol (0·55 g.) had m. p. 77—78°, $[\alpha]_D^{23}$ −4·6° (5% in EtOH), −1·4° (5% in $CHCl_3$). The infrared absorption of the propanol in CCl_4 was indistinguishable from that of the synthetic (±)-propanol described below.

(*b*) Reduction of the *epi*afzelechin compound (2·4 g.) with sodium (0·38 g.) as described above for the *epi*catechin analogue gave recovered (−)-*epi*afzelechin trimethyl ether (0·88 g., 37%), $[\alpha]_D^{21}$ −63° (2% in EtOH), and a phenolic fraction which was methylated and then chromatographed on acid-washed alumina. Elution with 7 : 3 benzene–light petroleum gave the propane (IX; R = H) (0·41 g., 17%), and elution with 85 : 15 benzene–chloroform gave a gummy fraction (0·58 g., 23%). The propanol (V; R = H) is readily soluble in hydrocarbons and other solvents (except water).

ω-*Acetoxy*-2 : 4 : 6-*trimethoxyacetophenone.*—ω-Chloro-2 : 4 : 6-trimethoxyacetophenone [27] (15·2 g., 87%) was prepared from 1 : 3 : 5-trimethoxybenzene (12 g.) and chloroacetonitrile (6 g.). The required phloroglucinol trimethyl ether was conveniently obtained by methylation of anhydrous phloroglucinol (30 g.) in acetone (*ca.* 250 c.c.) containing anhydrous potassium carbonate (110 g.) with dimethyl sulphate (75 c.c., *ca.* 3·3 equiv.), which was added in three equal portions at intervals of 2 hr. to the stirred, warm suspension. After the mixture had been heated for 6½ hr. (total) the crude product (34 g., 85%) was isolated in two fractions, m. p.s 40—42° and 43—46°, raised to 53° by recrystallisation from ethanol (prisms) (Found: C, 64·1; H, 7·1; OMe, 55·1. Calc. for $C_9H_{11}O_3$: C, 64·3; H, 7·2; 3OMe, 55·4%). ω-Chloro-2 : 4 : 6-trimethoxyacetophenone (14 g.), anhydrous potassium acetate (20 g.), acetic acid (25 c.c.), and acetic anhydride (10 c.c.) were heated for 2 hr. before filtration of the hot solution from potassium chloride (3·3 g., 78%) and evaporation of the solution under reduced pressure. The oil obtained by adding water to the brown residue rapidly solidified (14·9 g., 97%; m. p. 103—105°), and recrystallisation from ethyl acetate or ethyl acetate–hexane gave ω-*acetoxy*-2 : 4 : 6-*trimethoxyacetophenone* in rhombic prisms, m. p. 111—112° (Found: C, 58·2; H, 6·0; OMe, 34·7; Ac, 16·1. $C_{13}H_{16}O_6$ requires C, 58·3; H, 6·0; 3OMe, 34·3; Ac, 16·3%). The crude material was suitable for chalcone condensations.

3-(3 : 4-*Dimethoxyphenyl*)-1-(2 : 4 : 6-*trimethoxyphenyl*)*propane*-1 : 2-*dione* (XI; R = OMe). —Potassium hydroxide (4 g.) in water (4 c.c.) was added to ω-acetoxy-2 : 4 : 6-trimethoxyacetophenone (4 g.) and veratraldehyde (2·8 g.) in methanol (40 c.c.), and the solution was heated on a steam-bath for 3 hr. before being poured into water. The suspension was acidified with hydrochloric acid and extracted with chloroform, and the chloroform was removed after washing of the extract with aqueous sodium hydrogen carbonate and water. The oily residue from the evaporation was dissolved in a little ethyl acetate and diluted to incipient turbidity with hexane. Next day the deposit (2·55 g., 45%), m. p. 144—146°, was collected, and recrystallisation from methanol (*ca.* 80 c.c.) gave the *diketone* (XI; R = OMe) in pale yellow prisms (1·6 g.), m. p. 155—157° unchanged by recrystallisation in needles from aqueous acetone (Found: C, 64·3; H, 6·1; OMe, 41·0. $C_{20}H_{22}O_7$ requires C, 64·5; H, 5·9; 5OMe, 41·5%). Infrared absorptions were typical of enolised 1 : 2-diketones of this type: [18] OH absorption at 2·9 μ (in CCl_4) and 2·95 μ (in Nujol); >CO absorption at 5·98 μ (in CCl_4) and 6·0 μ (in Nujol). The compound was too sparingly soluble in carbon tetrachloride to afford optimum absorption curves.

[27] Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 168.

3-p-*Methoxyphenyl*-1-(2 : 4 : 6-*trimethoxyphenyl*)*propane*-1 : 2-*dione* (XI; R = H).—ω-Acetoxy-2 : 4 : 6-trimethoxyacetophenone (3·2 g.) and *p*-anisaldehyde (1·45 c.c.) were heated with aqueous-methanolic potassium hydroxide (3·2 g.), and the crude product (2·4 g.) was isolated as described above for the veratraldehyde analogue, and then washed with methanol to remove coloured impurities. Crystallisation from methanol (80 c.c.; charcoal) gave the diketone in pale yellow prisms (0·95 g.), m. p. 153° unchanged by recrystallisation in needles from aqueous acetone (lit.,[28] m. p. 144—145°) (Found: C, 65·9; H, 6·1; OMe, 36·6. Calc. for $C_{19}H_{20}O_6$: C, 66·3; H, 5·9; 4OMe, 36·0%). Infrared absorptions in Nujol: OH at 2·96 and >CO at 6·0 μ.

(±)-1-(3 : 4-*Dimethoxyphenyl*)-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-*ol*.—The diketone (XI; R = OMe) (0·6 g.) in ethanol (100 c.c.) was hydrogenated over Raney nickel (W4; *ca.* 0·6 g.) at 90—130° with hydrogen at 1000 lb./sq. in. for 6 hr. The filtrate from catalyst was evaporated under reduced pressure, and last traces of ethanol were removed by continuing the evaporation after the addition of benzene. The residue was dissolved in benzene (2—3 c.c.), and after the addition of a little hexane the (±)-*propanol* (0·5 g., 86%) crystallised in colourless prisms, m. p. 87—88° unchanged by recrystallisation (Found: C, 66·3; H, 7·3. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%). A carbon tetrachloride solution showed hydroxyl absorption at 2·75 μ and the absorption curve, recorded from 2 to 11·5 μ, was identical with curves obtained with the (−)- and the (+)-propanol (VII and V; R = OMe).

(±)-1-p-*Methoxyphenyl*-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-*ol*.—The diketone (XI; R = H) (0·6 g.) was hydrogenated as described for the pentamethoxy-diketone, and evaporation of the solvent left a viscous residue of the propanol. This was chromatographed on alumina and eluted with benzene (50 × 18 c.c.) and 9 : 1 benzene–chloroform (50 × 18 c.c.). The residues from the first 20 benzene–chloroform fractions solidified (m. p. *ca.* 60°) after several days, and solutions in carbon tetrachloride showed hydroxyl absorption at 2·77 μ, and the absorption curve (2—11·5 μ) was identical with that of the (−)-propanol (V; R = H) obtained from (−)-*epi*afzelechin trimethyl ether. The (±)-propanol crystallised in needles, m. p. 66°, by spontaneous evaporation of the carbon tetrachloride solution, but a satisfactory recrystallisation has not been achieved. The (±)-propanol dissolves readily in hexane, *cyclo*hexane, carbon tetrachloride, and other solvents except water.

(−)-epi*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—(−)-*epi*Catechin tetramethyl ether (2·5 g.) was esterified by reaction with phenylglyoxylyl chloride[29] (1·2 g., 1 mol.) according to the general procedure described by Dauben, Dickel, Jeger, and Prelog.[17] The 3-*phenylglyoxylate* (1 g., 30%) crystallised from ethanol in needles, m. p. 174—175° (after softening at 170°) unchanged by recrystallisation, $[\alpha]_D^{20}$ −29·2° (3% in $CHCl_3$) (Found: C, 67·3; H, 5·6. $C_{27}H_{26}O_6$ requires C, 67·8; H, 5·5%).

(+)-*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—The ester (1·55 g., 95%) was prepared from the (+)-catechin compound (1·2 g.) as described above for the epimer except that phenylglyoxylyl chloride (2·3 g., 4 mol.) was used to improve the yield, and the excess of acid was removed by washing with aqueous sodium hydrogen carbonate. The crude product was chromatographed on acid-washed alumina, and the ester was eluted with benzene and finally with benzene–chloroform (25%). Recrystallisation from ethanol gave the *phenylglyoxylate* in needles, m. p. 106—107° unchanged by recrystallisation, $[\alpha]_D^{20}$ +4·4° (4% in $CHCl_3$) (Found: C, 67·4; H, 5·3%).

(−)-*Atrolactic Acid from* (−)-epi*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—The phenylglyoxylate (0·7 g.) in dry benzene–ether was added dropwise to methylmagnesium iodide (4 mol.) in ether; a white precipitate appeared immediately and remained after 5 hours' boiling under reflux. The suspension was acidified with dilute acetic acid, and the organic layer was washed with water before evaporation under reduced pressure. The residue of atrolactate was dissolved in methanol–benzene containing potassium hydroxide (5%) and next day the solution was boiled under reflux for 4 hr. The solvent was removed under reduced pressure and an aqueous solution of the residue was exhaustively extracted with ether to remove *epi*catechin tetramethyl ether (*ca.* 0·5 g.). The aqueous layer was acidified and extraction of the solution with ether gave atrolactic acid (0·16 g.) contaminated with dark viscous material which was insoluble in light petroleum. Two recrystallisations from light petroleum gave atrolactic acid, needles, m. p. 85—93°, $[\alpha]_D^{20}$ −16·4° (2% in EtOH), containing 43% excess of the (−)-isomer.

[28] Hutchins, Motwani, Mudbhatkal, and Wheeler, *J.*, 1938, 1882.
[29] *Org. Synth.*, Coll. Vol. III, p. 114; Kharasch and Brown, *J. Amer. Chem. Soc.*, 1942, **64**, 329.

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(−)-*Atrolactic Acid from* (+)-*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—The (+)-catechin phenylglyoxylate (1·35 g.) was converted into the atrolactate and then hydrolysed as described above for the epimer. Two recrystallisations of the crude acid (0·28 g.) from light petroleum gave atrolactic acid hemihydrate, m. p. 85—90°, $[\alpha]_D^{21}$ −1·1° (28% in EtOH), containing 3% excess of the (−)-acid (Found: C, 61·8; H, 6·3. Calc. for $C_9H_{10}O_3.\frac{1}{2}H_2O$: C, 61·7; H, 6·3%). The experiment was repeated, because of the low optical activity, with (+)-catechin tetramethyl ether 3-phenylglyoxylate (3·7 g.) which gave similar results, and some possible sources of error were eliminated: hydrolysis was proved to be complete by quantitative recovery of catechin tetramethyl ether by exhaustive extraction with ether (no residue from the sixth extract), and contamination of the atrolactic acid with the lævorotatory catechin methyl ether was thus precluded. Contamination of the recrystallised atrolactic acid with the related glycol is precluded by elementary analysis (above), and the neutral fraction extracted by ether was shown by chromatography on alumina to consist only of catechin tetramethyl ether which was eluted with benzene and then with benzene containing increasing quantities of ether, the last traces being removed by benzene–ether (1 : 1). Ether (used in isolating the glycol [17]) removed nothing further from the column; the insolubility of the initial Grignard adduct probably prevented glycol formation from *epi*catechin and catechin atrolactates.

(−)-epi*Afzelechin trimethyl ether* 3-*phenylgloxylate* was prepared as described for the (+)-catechin analogue and crystallised from ethanol in needles, m. p. 123—124°, $[\alpha]_D^{20}$ −32·0° (5% in $CHCl_3$) (Found: C, 69·2; H, 5·4. $C_{26}H_{24}O_7$ requires C, 69·6; H, 5·4%). (−)-*epi*-Afzelechin trimethyl ether (1·0 g.) and phenylglyoxylyl chloride (2·1 g.) produced crude ester (1·35 g., 95%).

(−)-*Atrolactic Acid from* (−)epi-*Afzelechin Trimethyl Ether* 3-*Phenylglyoxylate*.—The ester (1·1 g.) was treated with methylmagnesium iodide (the initially insoluble Grignard adduct redissolved rapidly in this case), and the atrolactate was hydrolysed as described for the (−)-*epi*catechin analogue. Three crystallisations of the crude acid (0·13 g.) gave atrolactic acid, m. p. 107—111°, $[\alpha]_D^{20}$ −30·4° (5% in EtOH), containing 81% excess of the (−)-isomer. Recrystallisation of atrolactic acid, usually omitted,[3] was necessary in the present investigation because solutions of the crude acid were too dark for polarimetric examination.

The authors thank those who have assisted this investigation, and in particular Dr. A. R. H. Cole for his examination and interpretation of hydroxyl absorptions of *epi*catechin and catechin tetramethyl ethers, Monsanto Chemicals (Australia) Ltd., for the award of a scholarship (to A. V. R.), and Dr. W. G. C. Forsyth (Trinidad) and Mr. W. E. Hillis (Melbourne) respectively for gifts of (−)-*epi*catechin from cacao and (+)-catechin from *Uncaria gambir*. Analyses were performed by Miss B. Stevenson (Sydney) and the C.S.I.R.O. Microanalytical Service, Melbourne.

UNIVERSITY OF SYDNEY, NEW SOUTH WALES.
UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA.

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712. *Transport Numbers of Sodium and Potassium Iodides from Electromotive Force Measurements.*

By F. G. TORTO.

The electromotive forces (e_T) of the cells Ag–AgI|MI(c_R)|MI(c)|Ag–AgI, where M = Na or K, in the concentration range 0·1—0·5N, at 25° were measured. Electromotive forces (e) of the corresponding cells without transport were computed from existing activity coefficients, and the cation transport numbers obtained from the curve of e_T against e.

MEASUREMENTS of the e.m.f. of concentration cells with transport, in conjunction with those of the same cells without transport, are convenient for determining transport numbers, although the results are not as accurate as is possible with the moving-boundary method. Transport numbers of sodium and potassium iodides were determined [1] from

[1] Torto, Ph.D. Thesis, London University, 1947.

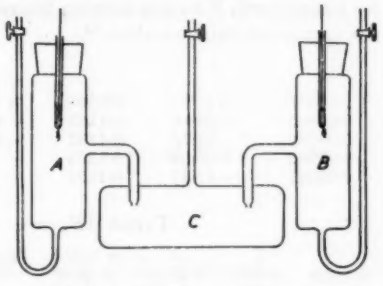
measurements of e.m.f. of the cells Ag–AgI|MI(c_R)|MI(c)|Ag–AgI, the electrolytes being the aqueous iodides. The e.m.f. of the corresponding cells without transport was obtained from Harned and Douglas's [2] activity coefficients for potassium and Robinson's [3] for sodium iodide. The cation transport numbers were obtained by applying Rutledge's differentiation procedure [4] to the curve obtained by plotting e_T for cells with transport against e for cells without transport.

Experimental

Materials.—" AnalaR " potassium iodide and sodium iodide were recrystallised thrice and four times, respectively, from distilled water, and dried at 120°. Solutions were boiled in a vacuum, allowed to cool in an atmosphere of purified hydrogen, and the iodide content determined gravimetrically or by titration with potassium iodate. Concentrations determined by the two methods agreed to within 0·05%.

Electrodes.—The silver–silver iodide electrodes were prepared as previously,[5] and with the rigid exclusion of oxygen from solutions and cell it was possible to obtain reproducibility of the order of 0·03—0·05 mv.

Cell and Filling Technique.—The cell is shown in the Figure. The electrodes, sealed into glass tubes, were mounted in well-fitting rubber bungs which were sealed in position with paraffin wax, the latter then being painted with collodion or cellulose acetate. The stopcocks were greased with petroleum jelly which had been boiled for several hours with frequently changed distilled water. In filling the cell, one limb A was rinsed with the lighter of the two solutions, forced in by hydrogen pressure, the limb B and the remainder of the cell being rinsed in a similar manner with the heavier solution. Purified hydrogen was then passed through the cell for about 30 min. With the cell inverted the lighter solution was forced into limb A, and the compartments B and C similarly filled with the heavier solution after turning the cell upright. The cell was placed in a thermostat at 25° (±0·02°); the thermostat and the potentiometer and its accessories stood on an equipotential metal foil surface.[6] The e.m.f. was measured at intervals of 10 min. until equilibrium was reached, usually in about 1 hr. To allow for the asymmetry between the electrodes, each measurement was repeated with the positions of the two electrodes in the two solutions reversed, and the two readings, which agreed to within 0·05—0·08 mv, averaged. Since the e.m.f. of this type of cell depends only on the solutions surrounding the electrodes, and not on the distribution of concentration gradients in the connecting solution, diffusion across the boundary between the two solutions should not affect the equilibrium e.m.f., which should therefore remain constant for considerable periods. (It remained constant for 36 hr. or more.) Moreover, replacement of the solution in compartment C in a cell set up in the normal way with *ca.* 0·2 and 0·3M-potassium iodide solutions with a solution containing approximately equal amounts of the two solutions had no effect on the equilibrium e.m.f. of 9·45 mv.



Discussion

Potassium Iodide.—The e.m.f. for solutions ranging between 0·05 and 0·5N was measured against a reference 0·1992N-solution. The lower concentration limit was fixed by the available activity-coefficient data, and the upper limit by the increasing solubility of silver iodide in iodide solutions [7] above 0·5N. The experimental e.m.f.s are given in Table 1*A*, and those for round concentrations obtained by interpolation are shown in

[2] Harned and Douglas, *J. Amer. Chem. Soc.*, 1926, **48**, 5095.
[3] Robinson, *ibid.*, 1935, **57**, 1161.
[4] Rutledge, *J. Math. Phys. M.I.T.*, 1929, **8**, 1; *Phys. Rev.*, 1932, **40**, 262.
[5] Partington and Torto, *J.*, 1948, 216.
[6] White, *J. Amer. Chem. Soc.*, 1914, **36**, 2011.
[7] Bates, *ibid.*, 1938, **60**, 2983.

column 4, Table 1*B*. The e.m.f.s of the corresponding cells without transport were obtained from Harned and Douglas's activity coefficients;[3] molalities were converted into molarities,[8] and activity coefficients at round concentrations read from a plot of f against $-\log c$. The values obtained (column 2, Table 1*B*) were employed in the expression $\varepsilon = -0{\cdot}1183 \log (c_1 f_1/c_2 f_2)$ to give the values of e in column 3, Table 1*B*.

From a large-scale plot[9] of $(e - e_T)$ against e, values of e_T were obtained at 5 mv intervals of e, and the function de_T/de evaluated by means of the Rutledge differentiation.[5] The values of de_T/de were plotted against e, and from this curve smoothed values of transport number n_e at round concentrations were obtained. As a check on the accuracy of this smoothing of the transport numbers the integral $\int_{e_R}^{e} de_T = e_T = \int_{e_R}^{e} n_e de$ was evaluated graphically from the plot of n_e against e. The values of e_T thus obtained are shown in column 5, Table 1*B*, and the deviation of these values from the experimental values under Δe_T. Apart from the value corresponding to $c = 0{\cdot}5$, Δe_T is within the limits of experimental error. The mean deviation of the plotted points from the smooth curve is less that $\pm 0{\cdot}002$, and this can be taken as a rough estimate of the mean error in the final transport numbers.

The final transport numbers are given in Table 1*C* together with the values obtained by Longsworth[10] by the moving-boundary method, and those obtained by Gelbach by the electromotive-force method.[11]

TABLE 1*A*.

c (moles/l.)	e_T (mv)	c (moles/l.)	e_T (mv)	c (moles/l.)	e_T (mv)	c (moles/l.)	e_T (mv)
0·06502	−26·46	0·1103	−13·52	0·1992	0·00	0·3862	+15·34
0·07080	−23·76	0·1203	−11·70	0·2306	+ 3·50	0·4352	+18·00
0·08302	−20·08	0·1355	− 8·86	0·2733	+ 7·29	0·4721	+19·93
0·09321	−17·47	0·1832	− 1·92	0·3401	+12·27	0·5007	+21·16

TABLE 1*B*.

c	f	e	e_T (exp.)	e_T (calc.)	Δe_T
0·7089	0·797	−48·57	−23·81	—	—
0·10	0·775	−32·26	−15·83	−15·82	0·01
0·15	0·748	−13·25	− 6·50	− 6·50	0·00
0·1992	0·729	0·00	0·00	—	—
0·25	0·715	+10·67	+ 5·27	+ 5·24	0·03
0·30	0·703	+19·17	+ 9·46	+ 9·42	0·04
0·35	0·694	+26·43	+12·99	+13·01	0·02
0·40	0·686	+32·69	+16·10	+16·06	0·04
0·45	0·681	+38·37	+18·81	+18·82	0·01
0·50	0·677	+43·48	+21·19	+21·29	0·10

TABLE 1*C*.

c	n_e	n_e (Longsworth [10])	n_e (Gelbach [11])
0·10	0·490	0·4883	0·4940
0·15	0·490	—	—
0·20	0·491	0·4887	0·4917
0·25	0·490	—	—
0·30	0·489	—	—
0·35	0·487	—	—
0·40	0·486	—	—
0·45	0·486	—	—
0·50	0·485	—	0·4878

Within the limits of the error inherent in our results, the agreement with the moving-boundary results is fair, and the slight increase in the transport number with concentration up to 0·2M found by Longsworth[10] is reproduced in our results.

Sodium Iodide.—The variable solutions had concentrations between 0·09 and 0·6N, and the reference solution was 0·1281N. The limits of concentration were fixed by similar considerations as in the previous case. The e.m.f.s of cells without transport were computed from Robinson's activity coefficients[4] obtained by the isopiestic vapour-pressure method. The manipulation of the data was carried out as for potassium iodide, and the results are given in Tables 2*A* and 2*B*, the figures having the same significance as those in corresponding columns of Tables 1*A* and 1*B*. The average value of Δe_T is 0·03 mv. As in the previous case the mean error in the final transport numbers, shown in column 1, Table 1*C*, is probably $\pm 0{\cdot}002$.

[8] Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold, New York. 1943, 556.
[9] Harned and Dreby, *J. Amer. Chem. Soc.*, 1939, **61**, 3113.
[10] Longsworth, *ibid.*, 1935, **57**, 1185.
[11] Gelbach, *ibid.*, 1933, **55**, 4857.

TABLE 2*A*.

c (moles/l.)	e_T (mv)	*c* (moles/l.)	e_T (mv)	*c* (moles/l.)	e_T (mv)	*c* (moles/l.)	e_T (mv)
0·08713	−7·00	0·1906	+ 7·23	0·2991	+15·40	0·4478	+22·79
0·1031	−3·84	0·2031	+ 8·30	0·3425	+17·93	0·5106	+25·16
0·1281	0·00	0·2478	+12·01	0·4017	+20·69	0·5884	+27·81
0·1534	+3·18			0·4201	+21·61		

TABLE 2*B*.

c	*f*	e	e_T (exp.)	e_T (calc.)	Δe_T
0·09935	0·788	−12·07	− 4·52	− 4·53	0·01
0·1281	0·773	0·00	0·00	0·00	0·00
0·1500	0·765	+ 7·54	+ 2·84	+ 2·84	0·00
0·1980	0·752	+20·95	+ 7·85	+ 7·85	0·00
0·2500	0·743	+32·32	+12·14	+12·09	0·05
0·2959	0·737	+40·57	+15·18	+15·16	0·02
0·3500	0·732	+48·84	+18·27	+18·22	0·05
0·4000	0·729	+55·49	+20·75	+20·68	0·07
0·4897	0·726	+65·67	+24·38	+24·31	0·07
0·6807	0·729	+82·81	+28·35	—	—

TABLE 2*C*.

c	n_e	n_e (Denison [12]) at 18°
0·05	—	0·381
0·10	0·375	0·376
0·15	0·375	—
0·20	0·374	—
0·25	0·373	—
0·30	0·371	—
0·35	0·368	—
0·40	0·364	—
0·45	0·359	—
0·50	0·354	—

It is obvious from Table 2*C* that the transport numbers increase as the solutions become more dilute, but approach a limiting value at high dilutions. In the absence of values at concentrations lower than 0·10N, it was not considered desirable to extrapolate the data to infinite dilution.

I thank Professor J. R. Partington, M.B.E., for advice.

QUEEN MARY COLLEGE, LONDON.
[Present Address.—UNIVERSITY COLLEGE OF GHANA, ACHIMOTA, GHANA.]

[*Received, March 29th,* 1957.]

[12] Denison, *Trans. Faraday Soc.*, 1909, **5**, 165.

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713. *The Reactions of Phosphorothiolates with Halogens.*

By C. J. M. STIRLING.

Chlorine and bromine react with triethyl and *S*-benzyl diethyl phosphorothiolate in anhydrous conditions to give the sulphenyl halides and phosphorohalidates. In water, alkanesulphonyl halides and alkyl halides are formed together with diethyl hydrogen phosphate. The mechanisms of the reactions are discussed; the aqueous reactions involve initial formation of sulphenyl halides.

SAVILLE [1] observed formation of ethanesulphonyl bromide in the reaction of bromine water with triethyl phosphorothiolate. In this paper, reactions of chlorine and of bromine with alkyl phosphorothiolates in aqueous and anhydrous conditions are reported.

Triethyl (I; R = Et) and *S*-benzyl diethyl phosphorothiolate (I; R = $PhCH_2$), in aqueous suspension, react rapidly with chlorine and with bromine, to give diethyl hydrogen phosphate and the appropriate alkanesulphonyl halide with minor amounts of the alkyl halide derived from the *S*-alkyl group (see Tables, p. 3601). When less chlorine than is required for complete reaction was used, the alkanesulphinic acid was isolated; and benzyl toluene-ω-thiolsulphonate (II; R = H) was obtained from the benzyl ester. Similar results have been obtained by Douglass and Johnson [2] on aqueous chlorination of thiolcarboxylic esters. Dibenzyl disulphide was an intermediate in the chlorination of benzyl thiolbenzoate, in addition to toluene-ω-sulphinic acid (III; R = H) and benzyl toluene-ω-thiolsulphonate. No dibenzyl disulphide, however, has been isolated from reactions with the phosphorus ester.

[1] Saville, *Chem. and Ind.*, 1956, 660.
[2] Douglass and Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 1486.

The formation of alkyl halides must occur by the displacement of sulphur at some stage. Halogenation of the intermediate, toluene-ω-sulphinic acid, gives mixtures of toluene-ω-sulphonyl halide and benzyl halide, similar to those obtained from the phosphorothiolate. It is probable, therefore, that S–C bond fission occurs in the final stage of

$(EtO)_2PO{\cdot}SR$ (I) $\quad Ph{\cdot}CH_2{\cdot}S{\cdot}SO_2{\cdot}CH_2{\cdot}C_6H_4R$ (II) $\quad R{\cdot}C_6H_4{\cdot}CH_2{\cdot}SO_2H$ (III)

the oxidation. Certain alkanesulphonyl halides, however, have been shown [3] to decompose at room temperature with the formation of the corresponding alkyl halide. Toluene-ω-sulphonyl halides have been found to be unstable and 30% of the benzyl halide obtained can be accounted for by their decomposition.

The origin of thiolsulphonate is less clear. Douglass and Johnson [4] suggested that the formation of benzyl toluene-ω-thiolsulphonate in the aqueous chlorination of benzyl thiocyanate was due to the disproportionation of toluene-ω-sulphinic acid which was also isolated from the reaction. However, toluene-ω-sulphinic acid does not disproportionate under the present experimental conditions: the only decomposition product which could be isolated was benzaldehyde.[5] Lee and Dougherty [6] have shown that benzyl toluene-ω-thiolsulphonate is obtained on the aqueous chlorination of dibenzyl disulphide. Evidence presented below, however, suggests that the formation of thiolsulphonate from disulphide (even if it is formed in the reaction with the phosphorus ester) is not a direct reaction but that S–S fission is the primary step. It was considered possible that thiolsulphonate is formed by the reaction of a sulphenyl halide, initially formed in the reaction, with sulphinic acid:

$$R{\cdot}SO_2H + RSX \longrightarrow R{\cdot}SO_2{\cdot}SR + HX \quad (X = Br \text{ or } Cl) \qquad (i)$$

Although silver sulphinates react with sulphenyl halides to give thiolsulphonates [7] no instance of the reaction with the free acid has been recorded. Toluene-ω-sulphenyl bromide has been found to react rapidly with toluene-ω-sulphinic acid with evolution of hydrogen bromide and formation of benzyl toluene-ω-thiolsulphonate. Proof that the reaction is not a disproportionation of the sulphinic acid has been obtained by the use of *p*-chlorotoluene-ω-sulphinic acid (III; R = Cl), benzyl *p*-chlorotoluene-ω-thiolsulphonate (II; R = Cl) being then isolated from reactions with both toluene-ω-sulphenyl chloride and toluene-ω-sulphenyl bromide. Thiolsulphonates are known [8] to be formed in the hydrolysis of sulphenyl halides, but no hydrolysis products could be detected in the experiments with the substituted sulphinic acid, despite the presence of water in the reaction mixtures.

The possibility that sulphenyl halides were formed in the aqueous halogenation of phosphorothiolates prompted an examination of the reactions in anhydrous conditions. Douglass and Osborne [9] have shown that with chlorine, anhydrous thiolcarboxylic and thiolsulphonic esters give acyl and sulphonyl chlorides respectively, together with sulphenyl trichlorides which were considered to arise by further chlorination of sulphenyl chlorides.[10] In the present work, treatment of the phosphorus esters in anhydrous carbon tetrachloride with two atoms of chlorine or bromine per mole of ester gave, except in the triethyl phosphorothiolate–chlorine reaction, the corresponding sulphenyl halides. These have been characterised by the formation of β-halogeno-sulphides [11] with ethylene or *cyclo*hexene. Ethanesulphenyl chloride could not be identified in the reaction of chlorine with the

[3] Truce and Vriesen, *J. Amer. Chem. Soc.*, 1953, **75**, 5032.
[4] Douglass and Johnson, *ibid.*, 1939, **61**, 2548.
[5] Cf. Kurzer and Powell, *J.*, 1952, 3728.
[6] Lee and Dougherty, *J. Org. Chem.*, 1940, **5**, 81.
[7] Child and Smiles, *J.*, 1926, 2696.
[8] Zinke and Eismayer, *Ber.*, 1918, **51**, 751.
[9] Douglass and Osborne, *J. Amer. Chem. Soc.*, 1953, **75**, 4582.
[10] Douglass, Brower, and Martin, *ibid.*, 1952, **74**, 5770.
[11] Cf. Fuson, Price, Bauman, Bullit, Hatchard, and Maynert, *J. Org. Chem.*, 1946, **11**, 469.

triethyl ester, but four atoms of chlorine per mole of ester gave ethanesulphenyl trichloride. The failure to obtain ethanesulphenyl chloride is considered to be due to preferential formation of the trichloride.[10] Toluene-ω-sulphenyl trichloride was similarly obtained from the benzyl ester:

$$(EtO)_2PO{\cdot}SR \xrightarrow{X_2} (EtO)_2PXO + RSX \xrightarrow{X_2} RSX_3 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Diethyl phosphorochloridate was isolated from the triethyl phosphorothiolate–chlorine reactions. In the remainder, the phosphorohalidate has been hydrolysed in alkali to give diethyl sodium phosphate. Anhydrous chlorination of benzyl toluene-ω-thiolsulphonate likewise gave a mixture of the sulphenyl and sulphonyl chloride directly, although reaction occurs less readily than with the phosphorus esters.

The high reactivity of aliphatic sulphenyl halides has, however, precluded their isolation from aqueous reactions of halogens with phosphorothiolates. Indirect evidence for their formation in aqueous reactions has been obtained in two ways. First, the partial aqueous chlorination of *S*-benzyl diethyl phosphorothiolate has been carried out in the presence of *p*-chlorotoluene-ω-sulphinic acid: isolation of benzyl *p*-chlorotoluene-ω-thiolsulphonate confirmed the view, not only that thiolsulphonate does not arise by disproportionation but also that it results from the attack on free sulphinic acid of a species in which the sulphur atom is in the +2 oxidation state. Secondly, aqueous chlorination of benzyl ethyl disulphide has been examined. If the oxidation of an unsymmetrical disulphide to a thiolsulphonate does not involve S–S fission, then only two products, both of which contain dissimilar alkyl groups, can result:

$$RS{\cdot}SR' \longrightarrow R{\cdot}SO_2{\cdot}SR' + RS{\cdot}SO_2R' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If, however, the initial reaction with chlorine causes S–S fission with the formation of sulphenyl chlorides, formation of thiolsulphonate according to (1) should give four products:

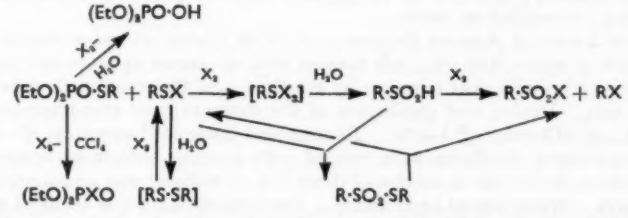
$$RS{\cdot}SR' \xrightarrow{Cl_2} RSCl + R'SCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$RSCl\ (R'SCl) \xrightarrow[2H_2O]{Cl_2} R{\cdot}SO_2H\ (R'{\cdot}SO_2H) \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$\left.\begin{matrix} R{\cdot}SO_2H \\ R'{\cdot}SO_2H \end{matrix}\right\} + \left.\begin{matrix} R'SCl \\ RSCl \end{matrix}\right\} \longrightarrow \left.\begin{matrix} R'S{\cdot}SO_2R & R{\cdot}S{\cdot}SO_2R' \\ RS{\cdot}SO_2R & R'{\cdot}S{\cdot}SO_2R' \end{matrix}\right\} + HCl \quad . \quad . \quad . \quad . \quad (6)$$

In two of the possible products, the alkyl groups are the same. Isolation of benzyl toluene-ω-thiolsulphonate, therefore, from the aqueous chlorination of benzyl ethyl disulphide, is considered to support this mechanism.

On the basis of the above considerations, the annexed scheme * is proposed for halogen-



ation of thiol esters not only in respect of this investigation but also of those referred to above. The isolation of dibenzyl disulphide from the aqueous chlorination of benzyl

* The intermediate formation of sulphenyl trihalide in aqueous reactions is speculative. An alternative route is:

$$RSX \xrightarrow{H_2O} RS{\cdot}OH \xrightarrow{X_2} RS{\cdot}OX \xrightarrow{H_2O} R{\cdot}SO_2H$$

Thiolsulphonate may then arise thus:

$$RS{\cdot}OH + R{\cdot}SO_2H \longrightarrow R{\cdot}SO_2{\cdot}SR$$

thiolbenzoate [2] may be explained by the hydrolysis of the intermediate sulphenyl chloride It has been confirmed that the anhydrous reaction gives benzoyl chloride and toluene-ω-sulphenyl chloride directly.

Experimental

The light petroleum used had b. p. 40—60°. Extracts were dried over $MgSO_4$.

Triethyl Phosphorothiolate.[12]—Diethyl hydrogen phosphite (55·2 g.) was added to a solution of sodium (9·2 g.) in absolute ethanol (300 ml.). Sulphur (12·8 g.) was added slowly with cooling, followed by ethyl bromide (44 g.). The solution was boiled under reflux for 2 hr., then the precipitated sodium bromide was filtered off. Distillation gave the ester (44 g.), b. p. 78·5—79°/1·3 mm., n_D^{25} 1·4570.

S-*Benzyl Diethyl Phosphorothiolate.*—The above procedure was used, with benzyl chloride instead of ethyl bromide. The product (79 g.) had b. p. 130°/0·2 mm., n_D^{25} 1·5229 (Found: C, 50·7; H, 6·7. Calc. for $C_{11}H_{17}O_3SP$: C, 50·8; H, 6·6%). Schrader [13] gives b. p. 165—170°/2 mm.

Reactions with Excess of Aqueous Chlorine.—(a) *With triethyl phosphorothiolate.* The ester (20 g.) was suspended in water (150 ml.) and chlorine was passed in with cooling and stirring at 0—5° until an excess was present. Excess of chlorine was removed in air and the suspension then extracted with benzene (3 × 50 ml.). The dried extracts were evaporated and distillation of the residue gave ethanesulphonyl chloride (12·2 g.), b. p. 76—79°/22 mm., n_D^{25} 1·4472, which, on treatment with *p*-toluidine, gave ethanesulphonyl-*p*-toluidine, m. p. and mixed m. p. 79—80° (80%). The aqueous extracts were basified with sodium carbonate and were evaporated to dryness. The residue was extracted with boiling absolute ethanol (400 ml.) and evaporation of the extracts gave diethyl sodium phosphate (13·6 g.) which was identified by its infrared spectrum and formation of the S-*benzylthiuronium salt*, m. p. 153—154°, as needles from acetone (Found: C, 44·8; H, 6·9. $C_{12}H_{21}O_4N_2SP$ requires C, 45·0; H, 6·6%).

(b) *With* S-*benzyl diethyl phosphorothiolate.* The ester (20 g.) was chlorinated as above, at <30°. Extraction was with chloroform (2 × 100 ml.). The dried extracts were evaporated and addition of light petroleum (100 ml.) to the residue precipitated toluene-ω-sulphonyl chloride (11·1 g.), which, after crystallisation from benzene–light petroleum, had m. p. 93° (Found: C, 43·9; H, 3·9. Calc. for $C_7H_7O_2ClS$: C, 44·1; H, 3·7%). Evaporation of the mother-liquors gave a further 0·8 g. of sulphonyl chloride, m. p. 86—91°. The residual solution was evaporated and the residue, which had an odour of benzyl chloride, was dissolved in methanol (25 ml.). Diethylamine (6 ml.) was added and the solution was refluxed for 2 hr. Methanol and diethylamine were distilled off and ether (100 ml.) was added. The suspension was extracted with 2N-hydrochloric acid (100 ml.), and the extracts were basified with sodium hydroxide and extracted with benzene. The benzene extracts were dried and evaporated. Methanol (25 ml.) and methyl iodide (10 ml.) were added and the solution was refluxed for 2 hr. Solvent was removed and the addition of ether (150 ml.) to the residue gave benzyldiethylmethylammonium iodide, m. p. and mixed m. p. 150·5—152° (from acetone) (0·2 g.). Hazard, Corteggiani, and Renard [14] give m. p. 150°. The aqueous extracts yielded sodium diethyl phosphate (10·8 g.), identified as before.

Reactions with Excess of Aqueous Bromine.—(a) *With triethyl phosphorothiolate.* The ester (12 g.), suspended in water (100 ml.), was treated with an excess of saturated bromine water at 0—5°. Excess of bromine was removed by ethylene, and the solution then extracted with ether (2 × 150 ml.). Drying and distillation of the extracts gave ethanesulphonyl bromide (6·8 g.), b. p. 81—83°/13 mm., n_D^{25} 1·5005. Johnson and Sprague [15] give b. p. 85—86°/18 mm., n_D^{25} 1·5010. The ethereal distillates were washed with aqueous sodium carbonate and dried. A solution of sodium methoxide in methanol (from 3 g. of sodium) was added and the mixture set aside for 2 days. Water (50 ml.) was added. The aqueous layer was acidified with halogen-free nitric acid: addition of aqueous silver nitrate gave a slight precipitate of silver bromide. The original aqueous extracts were evaporated to a small volume and treated with chlorine to remove bromide. Evaporation to dryness and extraction of the residue with ethanol gave sodium diethyl phosphate (5·7 g.).

[12] Cf. Foss, *Acta Chem. Scand.*, 1947, **1**, 8.
[13] Schrader, U.S.P. 2,597,534.
[14] Hazard, Corteggiani, and Renard, *Compt. rend.*, 1948, **227**, 1180.
[15] Johnson and Sprague, *J. Amer. Chem. Soc.*, 1936, **58**, 1348.

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(b) *With S-benzyl diethyl phosphorothiolate.* The ester (10 g.) was treated as in the preceding experiment and after the removal of excess of bromine the solution was extracted with chloroform (100 ml.). The dried extracts were evaporated and treatment of the residue with light petroleum (50 ml.) gave toluene-ω-sulphonyl bromide (3·6 g.), m. p. 78·5° (from light petroleum) (Found: C, 35·6; H, 3·2. Calc. for $C_7H_7O_2BrS$: C, 35·8; H, 3·0%). Holmberg [16] gives m. p. 79—80°. Treatment of the mother-liquors as before with diethylamine and methyl iodide gave crude benzyldiethylmethylammonium iodide (4 g.), m. p. 152° (from acetone) (1·3 g.; and 1·0 g., m. p. 145°). The original aqueous extracts were treated as before, to give sodium diethyl phosphate (2·4 g.).

The results of these experiments are shown in the Tables.

Products (mole/mole) obtained in aqueous chlorinations.

	$(EtO)_2PO{\cdot}OH$	$R{\cdot}SO_2Cl$	RCl
$(EtO)_2PO{\cdot}SEt$	0·77	0·94	—
$(EtO)_2PO{\cdot}S{\cdot}CH_2Ph$	0·80	0·82	0·02
$Ph{\cdot}CH_2{\cdot}SO_2H$	—	0·81	0·01

Products (mole/mole) obtained in aqueous brominations.

	$(EtO)_2PO{\cdot}OH$	$R{\cdot}SO_2Br$	RBr
$(EtO)_2PO{\cdot}SEt$	0·54	0·65	trace
$(EtO)_2PO{\cdot}S{\cdot}CH_2Ph$	0·35	0·40	0·29
$Ph{\cdot}CH_2{\cdot}SO_2H$	—	0·47	0·31

Partial Aqueous Chlorinations.—(a) *Triethyl phosphorothiolate.* The ester (15 g.) was suspended in water (100 ml.) and chlorine was passed in slowly for 5 min. at 0—5°. The solution was extracted with chloroform (2 × 15 ml.), and the extracts were extracted with ice-cold 10% aqueous sodium carbonate (2 × 10 ml.). The chloroform extracts were suspended in water and chlorine was again passed in for 5 min. The procedure was repeated several times and then the combined alkaline extracts were heated under reflux with benzyl chloride (2 g.) for 2 hr. The mixture was extracted with chloroform, and the dried extracts were evaporated. Ethanol (10 ml.) was added to the residue and, after several days, needles of benzyl ethyl sulphone separated, having m. p. and mixed m. p. 84° (from benzene–light petroleum).

(b) *S-Benzyl diethyl phosphorothiolate.* (i) Chlorine was passed into a suspension of the ester (10 g.) in water (200 ml.) until solid separated. The solid was filtered off and dissolved in benzene. The solution was extracted with 10% aqueous sodium carbonate (2 × 15 ml.), and treatment of the extracts with benzyl chloride as before gave dibenzyl sulphone, m. p. and mixed m. p. 150°.

(ii) The ester (10 g.), partly dissolved and partly suspended in light petroleum (100 ml.), was stirred with water (100 ml.) while chlorine was passed in at 5—10°. After the separation of an appreciable amount of solid, the mixture was filtered and the filtrate was treated with excess of chlorine. The mixture was filtered again and the combined residues were dried and treated with ether (75 ml.). The undissolved portion (0·2 g.) was benzyl toluene-ω-thiolsulphonate, m. p. and mixed m. p. 107°. Aniline (10 g.) was added to the solution which was kept overnight over saturated aqueous sodium hydrogen carbonate. The ethereal solution was extracted with dilute hydrochloric acid and then with 2N-sodium hydroxide (3 × 50 ml.). Acidification of the alkaline extracts gave toluene-ω-sulphonanilide (3·8 g.), m. p. and mixed m. p. 103°. The ethereal solution was evaporated and the residue, on treatment with ethanol, gave a further amount of benzyl toluene-ω-thiolsulphonate (0·7 g.), m. p. and mixed m. p. 107°.

Reactions with Sulphinic Acids.—Toluene-ω-sulphinic acid. Reduction of toluene-ω-sulphonyl chloride with aqueous sodium sulphite [17] gave the acid, m. p. 59—60·5°, in 45% yield. Holmberg [16] gives m. p. 61—63°.

(a) *Halogenation.* Aqueous chlorination and bromination of toluene-ω-sulphinic acid were carried out in the same way as the halogenations of the phosphorus esters. The results are in the Tables.

(b) *Stability in acid solutions.* Toluene-ω-sulphinic acid (1 g.) was added to a 50 ml. portion of the aqueous extracts of a reaction mixture from the complete chlorination of the benzyl ester. After being stirred for 30 min. at 100°, the suspension was extracted with chloroform

[16] Holmberg, *Arkiv Kemi, Min., Geol.*, 1940, **14**, *A*, No. 8.
[17] Cf. Smiles and Bere, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 7.

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(2 × 15 ml.). The extracts were washed with saturated aqueous sodium hydrogen carbonate and evaporated. A small amount of dark material remained but no benzyl toluene-ω-thiolsulphonate could be obtained from it. Acidification of the alkaline washings gave the sulphinic acid (0·6 g.), m. p. and mixed m. p. 59—60°. Similar experiments were carried out with 2N-hydrochloric and -hydrobromic acid at 20° for 24 hr. In each case more than 50% of the acid was recovered and no thiolsulphonate was isolated. A trace of benzaldehyde was identified in the neutral residue from the experiment with hydrobromic acid as the semicarbazone, m. p. and mixed m. p. 210—213°. There was no evidence for the formation of alkyl halides in these experiments.

(c) *Reaction with toluene-ω-sulphenyl bromide.* A solution of the sulphenyl bromide in benzene (100 ml.) was prepared from toluene-ω-thiol (1 g.) and *N*-bromosuccinimide (1·7 g.).[18] Toluene-ω-sulphinic acid (1·8 g.) and water (50 ml.) were added to the solution which was vigorously shaken. The colour of the suspension was rapidly discharged and after 1 hr. the layers were separated. The benzene layer was washed with sodium carbonate and evaporated. Addition of ethanol to the residue gave benzyl toluene-ω-thiolsulphonate (1·3 g.), m. p. and mixed m. p. 106°.

p-*Chlorotoluene-ω-sulphinic Acid.*—*p*-Chlorotoluene-ω-sulphonyl chloride was prepared by chlorination[15] of an aqueous solution of *S*-*p*-chlorobenzylthiuronium hydrochloride and had m. p. 93—94° (from benzene–light petroleum) (Found: Cl, 31·2. Calc. for $C_7H_6O_2Cl_2S$: Cl, 31·5%). Jackson and White[19] give m. p. 85·5°. Reduction of the sulphonyl chloride with aqueous sodium sulphite gave p-*chlorotoluene-ω-sulphinic acid* as plates, m. p. 104° (from ether) (Found: C, 44·0; H, 3·9; S, 17·0. $C_7H_7O_2ClS$ requires S, 16·8%). A solution of the acid in aqueous sodium carbonate on treatment with *p*-chlorobenzyl chloride at 100° gave di-(4-chlorobenzyl) sulphone, m. p. 246—247° (from acetone). Overberger, Lighthelm, and Swire[20] give m. p. 246—247°.

(a) *Reaction with toluene-ω-sulphenyl chloride.* Dibenzyl disulphide (2 g.), in carbon tetrachloride (20 ml.), was added dropwise with stirring to a solution of sulphuryl chloride (1·1 g.) in carbon tetrachloride (30 ml.) at −30°. The mixture was warmed to 20° and *p*-chlorotoluene-ω-sulphinic acid (2 g.) was added. The mixture was thoroughly shaken and water (25 ml.) was added. When the colour of the mixture had almost disappeared, the layers were separated and the organic layer was washed with aqueous sodium carbonate and dried. Solvent was removed and crystallisation of the residue gave *benzyl* p-*chlorotoluene-ω-thiolsulphonate* as needles, m. p. 118° (from ethanol) (Found: C, 53·3; H, 4·4. $C_{14}H_{13}O_2ClS_2$ requires C, 53·8; H, 4·2%).

(b) *Reaction with toluene-ω-sulphenyl bromide.* The experiment was carried out as described for toluene-ω-sulphinic acid. Crude benzyl *p*-chlorotoluene-ω-thiolsulphonate (1·2 g.), m. p. 112°, was obtained. Crystallisation from ethanol raised the m. p. to 118°, alone or mixed with the compound obtained in the previous experiment.

(c) *Partial chlorination of* S-*benzyl diethyl phosphorothiolate in the presence of* p-*chlorotoluene-ω-sulphinic acid.* Partial chlorination of the benzyl ester was repeated except that *p*-chlorotoluene-ω-sulphinic acid (15 g.) was added. The residue from the evaporation of the chloroform extracts, after the removal of the excess of aniline and the mixture of sulphonanilides, gave, on treatment with ethanol, benzyl *p*-chlorotoluene-ω-thiolsulphonate (0·3 g.), m. p. and mixed m. p. 116°.

Reactions with Anhydrous Chlorine.—(a) *With* S-*benzyl diethyl phosphorothiolate.* (i) The ester (20 g.), in anhydrous carbon tetrachloride (100 ml.), was shaken at 20° with a solution of chlorine (5·5 g.) in carbon tetrachloride (100 ml.), and set aside for 15 min. Ethylene was passed into the yellow solution for 45 min. during which time the colour faded. After being washed with 10% aqueous sodium hydroxide, the solution was dried and evaporated. A portion (2 g.) of the dark residue (14·2 g.) was heated with 30% hydrogen peroxide in acetic acid, to give benzyl 2-chloroethyl sulphone which crystallised from benzene–light petroleum as plates, m. p. 97° (Found: C, 49·6; H, 5·5. Calc. for $C_9H_{11}O_2ClS$: C. 49·4; H, 5·1%). Heyna and Riemenschneider[21] give m. p. 96°. The remainder of the residue was distilled to a purple oil (9·6 g.), b. p. 144—148°/13 mm., n_D^{25} 1·5564, which, on treatment with 20% aqueous

[18] Emde, G.P. 804,572.
[19] Jackson and White, *Amer. Chem. J.*, 1880, **2**, 158.
[20] Overberger, Lighthelm, and Swire, *J. Amer. Chem. Soc.*, 1950, **72**, 2856.
[21] Heyna and Riemenschneider, G.P. 887,505.

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chloramine-T gave *S*-benzyl-*S*-2-chloroethyl-*N*-*p*-toluenesulphonylsulphidimine, m. p. 134° (from ethanol) (Found: N, 4·1. Calc. for $C_{16}H_{18}O_2NClS_2$: N, 3·9%). Dawson [22] gives m. p. 133—134°.

(ii) The ester (15 g.) in carbon tetrachloride (60 ml.) at −20° was treated with chlorine (8·2 g., 4 atom-equivs.) in carbon tetrachloride (90 ml.). The solid which separated was rapidly filtered off on a chilled filter and when added to ice-cold 10% aqueous sodium carbonate (25 ml.) reacted with vigorous evolution of carbon dioxide. The solution was heated with benzyl chloride, giving dibenzyl sulphone (0·35 g.), m. p. and mixed m. p. 149·5°.

(b) *With triethyl phosphorothiolate.* Treatment of the ester with 2 atom-equivs. of chlorine and subsequent addition of ethylene or *cyclo*hexene failed to give identifiable products. The ester (10 g.) was treated as in the preceding experiment with 4 atoms of chlorine per mole. The solid which separated, on treatment with sodium carbonate and benzyl chloride as before, gave benzyl ethyl sulphone (1·2 g.), m. p. 75°. Crystallisation from benzene–light petroleum raised the m. p. to 84° (and mixed m. p.). The filtrate was evaporated and distillation of the residue gave a fraction (4·2 g.), b. p. 91—93°/17 mm., n_D^{25} 1·4247, which, on treatment with aniline in benzene solution, gave aniline hydrochloride, m. p. 197°, and diethyl phenylphosphoramidate, m. p. and mixed m. p. 94—95°.

(c) *With benzyl toluene-ω-thiolsulphonate.* The following method for the preparation of the ester was superior to Hinsberg's: [23] toluene-ω-sulphinic acid (18 g.), in carbon tetrachloride (150 ml.), was added to a solution of toluene-ω-sulphenyl chloride [from dibenzyl disulphide (20 g.) and chlorine (6 g.)] in carbon tetrachloride (150 ml.). The solution was agitated under reduced pressure and the ester was precipitated as needles (30 g.) which, after being washed with light petroleum, had m. p. and mixed m. p. 107·5°.

(i) The ester (8 g.), in alcohol-free anhydrous chloroform (50 ml.), was treated with chlorine (2 g.) in carbon tetrachloride (30 ml.). After the passage of ethylene (1 hr.) solvent was removed and light petroleum was added to the residue. The solid which separated was treated with aniline in benzene as above, to give toluene-ω-sulphonanilide (1·2 g.), m. p. and mixed m. p. 98—100°. Starting material (0·5 g.), m. p. and mixed m. p. 106°, was recovered. The light petroleum mother-liquors were evaporated and treatment of the residue with hydrogen peroxide in acetic acid gave benzyl 2-chloroethyl sulphone (0·2 g.), m. p. 89° raised on crystallisation to 94—95° alone or mixed with an authentic specimen.

(ii) The preceding experiment was repeated except that *cyclo*hexene (10 ml.) was used in place of ethylene. Toluene-ω-sulphonanilide (3·3 g.), m. p. and mixed m. p. 99—101°, was obtained and starting-material (3·1 g.) was recovered. The residue from the evaporation of the light petroleum mother-liquors, on treatment with hydrogen peroxide, gave *benzyl 2-chlorocyclohexyl sulphone* (0·3 g.), m. p. 106°, raised to 108—109° on crystallisation from ethanol (Found: Cl, 12·7; S, 12·0. $C_{13}H_{17}O_3ClS$ requires Cl, 13·0; S, 11·8%).

(d) *With benzyl thiolbenzoate.* The ester (12 g.) was treated with two atomic proportions of chlorine in carbon tetrachloride. After the passage of ethylene (30 min.), the solution was evaporated and distillation of the residue gave benzoyl chloride (5·1 g.), b. p. 81°/13 mm. (benzamide, m. p. and mixed m. p. 127°), and benzyl 2-chloroethyl sulphide (5·7 g.), b. p. 148—153°/13 mm., n_D^{25} 1·5712 (sulphone, m. p. and mixed m. p. 97°; *N*-*p*-toluenesulphonylsulphidimine, m. p. and mixed m. p. 134°).

Reactions with Anhydrous Bromine.—(a) *With triethyl phosphorothiolate.* The ester (15 g.) in carbon tetrachloride (100 ml.) was treated with bromine (12·1 g.) in carbon tetrachloride (80 ml.), and ethylene was passed into the solution for 1 hr. The solution was extracted with 10% aqueous sodium carbonate and, after being washed and dried, solvent was removed. Distillation of the residue gave impure 2-bromoethyl ethyl sulphide (9·8 g.), b. p. 68—71°/15 mm., n_D^{25} 1·5219 (Found: C, 27·7; H, 5·3. Calc. for C_4H_9BrS: C, 28·4; H, 5·3%). Steinkopf, Herold, and Stöhr [24] give b. p. 83—86°/ 29 mm. Treatment of the product with chloramine-T gave the sulphidimine, m. p. 147—148°, needles from ethanol (Found: N, 4·1. Calc. for $C_{11}H_{16}O_2NBrS_2$: N, 4·1%). Dawson [22] gives m. p. 146°.

(b) *With S-benzyl diethyl phosphorothiolate.* The ester (20 g.), in carbon tetrachloride (100 ml.), was treated with a solution of bromine (12·3 g.) in carbon tetrachloride (100 ml.). The

[22] Dawson, *J. Amer. Chem. Soc.*, 1947, **69**, 968.
[23] Hinsberg, *Ber.*, 1908, **41**, 2836.
[24] Steinkopf, Herold, and Stöhr, *Ber.*, 1920, **53**, 1007.

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mixture was treated as in the preceding experiment and a portion (2 g.) of the residue (22 g.), after the removal of solvent, was oxidised with 5% aqueous potassium permanganate to give *benzyl 2-bromoethyl sulphone*, m. p. 134—135° (plates from benzene–light petroleum) undepressed on admixture with the sulphone obtained by the oxidation of benzyl 2-bromoethyl sulphide [25] with hydrogen peroxide in acetic acid (Found: C, 41·2; H, 4·6. $C_9H_{11}O_2BrS$ requires C, 41·1; H, 4·2%). Distillation of the remainder of the residue gave no benzyl 2-bromoethyl sulphide, but a fraction, b. p. 90°/0·2 mm., on treatment with permanganate in acetic acid, gave dibenzyl sulphone, m. p. and mixed m. p. 151°. The experiment was repeated and oxidation of the entire residue gave benzyl 2-bromoethyl sulphone (8·8 g.), m. p. and mixed m. p. 131—132°.

In each of the above experiments with phosphorus esters and anhydrous halogens, sodium diethyl phosphate was isolated from the alkaline extracts.

Benzyl Ethyl Disulphide.—A mixture of ethanethiol (40 g.) and toluene-ω-thiol (40 g.), in carbon tetrachloride (300 ml.), was cooled to 0° and a slight excess of a 10% solution of bromine in carbon tetrachloride was added with stirring. The solution was washed with aqueous sodium carbonate and dried. Removal of the solvent and fractional distillation of the residue gave *benzyl ethyl disulphide* (17 g.), b. p. 75°/0·1 mm., n_D^{25} 1·5820 (Found: C, 58·6; H, 7·0. $C_9H_{12}S_2$ requires C, 58·7; H 6·6%). During 2 weeks, the product deposited a small amount of dibenzyl disulphide and samples used in the experiment below were redistilled just before use.

Partial Aqueous Chlorination of Benzyl Ethyl Disulphide.—Chlorine was passed slowly into a suspension of benzyl ethyl disulphide (15 g.), in water (150 ml.), at 0—5° until solid separated. The suspension was extracted with chloroform and the dried extracts were evaporated. The residue was treated as before with aniline to remove sulphonyl halides, and the neutral material crystallised from ethanol, giving needles of benzyl toluene-ω-thiolsulphonate (0·7 g.), m. p. and mixed m. p. 107—108°.

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[25] Schneider, *Chem. Ber.*, 1951, **84**, 911.

714. *The Structure of Dialkylthiopyrophosphonates and Related Compounds.*

By D. G. COE, B. J. PERRY, and R. K. BROWN.

Dialkyl dialkylthiopyrophosphonates have been prepared by the action of hydrogen sulphide and pyridine on alkyl alkylphosphonochloridates. The infrared spectra of these compounds indicate a thiono-structure as does that of the analogous tetraethyl thiopyrophosphate. Tetraethyl selenopyrophosphate also exhibits a selenono-structure.

ORGANIC pyrophosphates are now of considerable interest as potential insecticides and the possibility of improving their insecticidal properties by incorporation of a sulphur atom has led to the synthesis of several thiopyrophosphates.[1] A series of dialkyl dialkylthio-

$$2(RO)R'P(O)Cl + H_2S + 2C_5H_5N \longrightarrow (RO)R'P(O)\cdot O\cdot P(S)(OR)R' + 2C_5H_5N,HCl \quad . \quad (1)$$

pyrophosphonates has now been prepared from the appropriate alkyl alkylphosphonochloridate essentially by the procedure used by Fiszer *et al.*[1] for the preparation of thiopyrophosphates. The analogous dialkyl dialkylpyrophosphonates were also prepared, by the action of water on the alkyl alkylphosphonochloridates, pyridine being used to remove hydrogen chloride :

$$(RO)R'P(O)Cl \xrightarrow{H_2O} (RO)R'P(O)OH \xrightarrow{(RO)R'P(O)Cl} (RO)R'P(O)\cdot O\cdot P(O)(OR)R' \quad . \quad (2)$$

[1] Fiszer, Michalski, and Wieczorkowski, *Roczniki Chem.*, 1953, **27**, 482; Kosolapoff, U.S.P., 2,582,204 and 2,567,154/1951; Harman and Stiles, U.S.P. 2,630,450/1953; Schrader and Muhlman, G.P. 848,812/1952; Arbusov, Alinsov, Zvereva, Neklesova, and Kudrina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1954, 1038.

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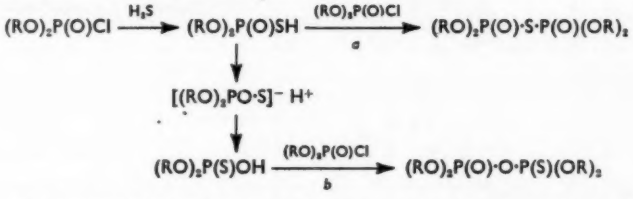
Tetraethyl thiopyrophosphate was prepared by two routes—the " hydrogen sulphide method " (Fiszer *et al.*[1]), and from diethyl phosphite and sulphur monochloride in presence of pyridine (Harman and Stiles [1]). The products were identical. Tetraethyl selenopyrophosphate was prepared by Michalski and Wieczorkowski's method.[2]

The phosphonochloridates were prepared from dialkyl alkylphosphonates by Arbusov's method followed by treatment with carbonyl chloride : [3]

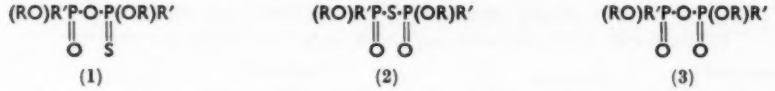
$$\left.\begin{array}{l}(RO)_3P + R'I \longrightarrow (RO)_2R'PO + RI \\ (RO)_2R'PO + COCl_2 \longrightarrow (RO)R'P(O)Cl + CO_2 + RCl\end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$(EtO)_2P(O)\cdot O\cdot P(OEt)_2 + S \longrightarrow (EtO)_2P(O)\cdot O\cdot P(S)(OEt)_2 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

On the basis of the synthetical route (4) used, Arbusov and Arbusov [4] assigned to tetraethyl thiopyrophosphate the thiono-structure shown. Most subsequent workers [1] have assumed this to be correct although the synthesis was often ambiguous. Fiszer *et al.*[1] considered that their " hydrogen sulphide " route would lead more logically to the bis(dialkoxyphosphinyl) sulphide structure as in route (*a*). However, the ionic nature of the dialkyl hydrogen phosphorothiolate would permit reaction in either form. The same considerations apply to the similar synthesis of the dialkylthiopyrophosphonates, and are equally applicable in a reverse sense if a sodium phosphorothionate (or selenonate) is used as an intermediate. In order to elucidate the structure of these compounds their infrared spectra have been examined.



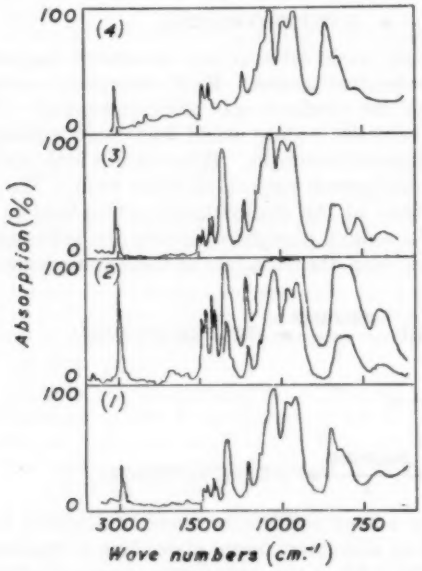
Since no results are available allocating a band position for absorption arising from a P–S–P linkage it has been necessary to find an alternative means of deciding to what extent this group may be present in any molecule. All of the compounds examined exhibit a band due to the P=S group but since it is broad and frequently overlaps others it is not a satisfactory basis for calculations. In compounds of type (1) the absorbance due to the P=O band should be approximately half that of compounds (2) and (3).



The relative change in intensity can be estimated as readily from $\int I_\lambda d\lambda$ [where I is $\log_{10}(T_0/T)$] as from $\int I_\nu d\nu$ since these are connected by constant factors for a given band.[5] The spectrometer resolution was sufficiently great to satisfy Ramsay's [5] criterion such that the apparent integrated absorption coefficients should not differ from their true values by more than 5%. Use being made of this fact, the absorbance of the P=O stretching vibration (1300—1200 cm.$^{-1}$) in the dialkylthiopyrophosphonates and the thio- and seleno-pyrophosphates has been compared with that in the fully oxygenated compound. Since the spectra were obtained from contact films it has been necessary to determine the relative absorbance of the P=O band by comparing its absorption with that of a band not appreciably affected by introduction of a sulphur atom; for this purpose the alkoxy–phosphorus

[2] Michalski and Wieczorkowski, *Roczniki Chem.*, 1954, **28**, 239.
[3] Ford-Moore, Lermit, and Stratford, *J.*, 1953, 1777.
[4] A. and B. Arbusov, *J. prakt. Chem.*, 1931, **130**, 103.
[5] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72.

(EtO–P or Pr^iO–P) stretching vibration (*ca.* 1175 or 1110 cm.$^{-1}$, respectively) has been chosen and allocated an absorbance of unity. Thus, in a specimen of tetraethyl thiopyrophosphate, the relative values of $\int I_\lambda d\lambda$ at 1164 cm.$^{-1}$ (EtO–P) and 1261 cm.$^{-1}$ (P=O) are 27 and 81, respectively, giving a value for the relative absorbance of the P=O stretching vibration of 3. In the spectrum of tetraethyl pyrophosphate the corresponding figures are 33 and 220 giving a relative absorbance of 6·6; *i.e.* the degree of absorbance due to P=O in the sulphur-containing compound is 3/6·6 = 0·46 of that of the oxygenated compound.



Infrared spectra of:
(1) *Tetraethyl thionopyrophosphate.*
(2) *Tetraethyl selenonopyrophosphate.*
(3) *Tetraethyl pyrophosphate.*
(4) *Tetraethyl pyrophosphorothionate.*

Table 1 gives the value of the relative absorbance of the P=O band determined as shown above and the degree of P=O absorption for the thio- and seleno-compounds prepared. The figures for $(EtO)_2P(S)\cdot O\cdot P(S)(OEt)_2$ are also given

TABLE 1. *The relative absorbance (A) of the* P=O *band and the degree of* P=O *absorption (B) in compounds of the type* R′R″P(X)·O·P(O)R′R″.

Compound			Spectrum			Compound			Spectrum		
R′	R″	X	no.	*A*	*B*	R′	R″	X	no.	*A*	*B*
EtO	EtO	S	1	3·0	0·46	EtO	Et	S	7	3·8	0·49
EtO	EtO	Se	2	3·2	0·48	EtO	Et	O	8	7·7	1·0
EtO	EtO	O	3	6·6	1·00	Pr^iO	Me	S	9	3·1	0·53
$(EtO)_2P(S)\cdot O\cdot P(S)(OEt)_2$			4	0·3	0·05	Pr^iO	Me	O	10	5·8	1·00
EtO	Me	S	5	3·8	0·44	Pr^iO	Et	S	11	2·7	0·50
EtO	Me	O	6	8·7	1·00	Pr^iO	Et	O	12	5·4	1·00

The figures for the sulphur and selenium compounds are sufficiently close to 0·5 to show that the compounds exist almost exclusively in the thiono- (selenono-) structure and that the thiolo- (selenolo-) form cannot be present to any marked extent.

EXPERIMENTAL

Alkyl Alkylphosphonochloridates.—Carbonyl chloride, dried by passage through sulphuric acid, was passed for 24 hr. into the dialkyl alkylphosphonate at <25°. After the mixture had been degassed at room temperature, the alkyl alkylphosphonochloridate was distilled at <50°. The following esters were thus obtained: ethyl methylphosphonochloridate, b. p. 37°/0·7 mm.,

n_D^{25} 1·4320; ethyl ethylphosphonochloridate, b. p. 43°/1 mm., n_D^{25} 1·4362; *iso*propyl methylphosphonochloridate, b. p. 40°/1 mm., n_D^{25} 1·4285; *iso*propyl ethylphosphonochloridate, b. p. 38°/1 mm., n_D^{25} 1·4322.

Tetraethyl Thionopyrophosphate.—This ester was prepared by the following modification of the method of Fiszer *et al.*[1] Diethyl phosphorochloridate (0·2 mole) was added dropwise with stirring and cooling to dry pyridine (0·3 mole) in benzene (100 ml.). Dry hydrogen sulphide was passed into the mixture for 4 hr. After the pyridinium chloride had been filtered off the benzene solution was evaporated under reduced pressure and finally warmed to 80°/0·1 mm., at which pressure the last traces of hydrochloride sublimed. Subsequent distillation afforded tetraethyl thionopyrophosphate (0·038 mole, 38%), b. p. 86—88°/5 × 10^{-4} mm., n_D^{20} 1·4505 (Fiszer *et al.* reported b. p. 120—122°/0·5 mm., n_D^{25} 1·4495).

A second specimen, prepared by Harman and Stiles's method,[1] was obtained in 68% yield, b. p. 81°/5 × 10^{-4} mm., n_D^{21} 1·4494, and had an infrared spectrum similar to that of the first.

Diethyl Dimethylthionopyrophosphonate.—Hydrogen sulphide was passed though a stirred solution of ethyl methylphosphonochloridate (33 g., 0·21 mole) and pyridine (26·8 g., 0·33 mole) in benzene at 10—15° for several hours. After filtration the product was worked up as described above. Fractional distillation of the crude product gave *diethyl dimethylthionopyrophosphonate* (10·5 g., 44%), b. p. 73—74°/3·5 × 10^{-4} mm., n_D^{20} 1·4679 (Found: C, 29·4; H, 6·75. $C_6H_{16}O_4P_2S$ requires C, 29·3; H, 6·55%).

Diethyl Diethylthiopyrophosphonate.—Ethyl ethylphosphonochloridate (35 g., 0·22 mole) in pyridine and benzene was treated with hydrogen sulphide. Fractional distillation of the crude product gave *diethyl diethylthionopyrophosphonate* (23 g., 70%), b. p. 84°/10^{-3} mm., n_D^{25} 1·4652 (Found: C, 35·0; H, 7·7. $C_8H_{20}O_4P_2S$ requires C, 35·0; H, 7·35%).

Diisopropyl Dimethylthionopyrophosphonate.—Similarly prepared, *diisopropyl dimethylthionopyrophosphonate* (9·5 g., 35%) had b. p. 74—75°/2 × 10^{-3} mm., n_D^{20} 1·4616 (Found: C, 35·0; H, 7·7. $C_8H_{20}O_4P_2S$ requires C, 35·0; H, 7·3%).

Diisopropyl Diethylthionopyrophosphonate.—*Diisopropyl diethylthionopyrophosphonate* was obtained from *iso*propyl ethylphosphonochloridate (40 g., 0·24 mole) in 55% yield, b. p. 90°/7 × 10^{-4} mm., n_D^{20} 1·4516 (Found: C, 39·5; H, 7·95. $C_{10}H_{24}O_4P_2S$ requires C, 39·7; H, 8·0%).

Tetraethyl Selenonopyrophosphate.—Tetraethyl selenonopyrophosphate was obtained in 55% yield (0·2 molar scale) by Michalski and Wieczorkowski's method;[2] it had b. p. 95°/6 × 10^{-4} mm., n_D^{25} 1·4582.

Tetraethyl Pyrophosphorothionate.—Commercial material was fractionally distilled to give a sample, b. p. 98°/4 × 10^{-4} mm., n_D^{20} 1·4761.

Dialkyl Dialkylpyrophosphonates.—The esters detailed in Table 2 were prepared on a 0·2 molar scale: water (0·1 mole) and pyridine (0·1 mole) were added dropwise to a stirred solution of alkyl alkylphosphonochloridate (0·2 mole) and pyridine (0·1 mole) in benzene at 0°. Stirring was continued for an hour after completion of the addition and the base hydrochloride then removed by filtration and sublimation as previously described; distillation then afforded the dialkyl dialkylpyrophosphonate.

TABLE 2. *Dialkyl dialkylpyrophosphonates* (RO)R'P(O)·O·P(O)(OR)R'.

						Analysis: Found,		Calc.,	
R	R'	Yield, %	B. p./mm.	n (t°)	Formula	C	H	C	H
Et	Me	85	68—70°/3·5 × 10^{-4}	1·4360 (20)	$C_6H_{16}O_5P_2$	31·5	6·9	31·3	7·0
Et	Et	60	70°/7 × 10^{-4}	1·4302 (25)	$C_8H_{20}O_5P_2$	37·3	7·9	37·2	7·75
Pr^i	Me	51	78—80°/7 × 10^{-3}	1·4270 (25)	$C_8H_{20}O_5P_2$	37·5	8·0	37·2	7·75
Pr^i	Et	55	65—66°/6 × 10^{-4}	1·4304 (25)	$C_{10}H_{24}O_5P_2$	41·8	8·4	41·95	8·45

Spectra.—Those presented in the Figure were obtained by using a Perkin–Elmer model 21 double-beam recording spectrophotometer.

The authors acknowledge helpful discussions with Dr. R. B. Harvey and Dr. J. Mayhood on the infrared spectra, and thank The Defence Research Board of Canada for permission to publish this paper.

SUFFIELD EXPERIMENTAL STATION, RALSTON, ALBERTA. [*Received, November 30th,* 1956.]

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715. *The Kinetics of Catalytic Polymerisations. Part VI.* Polymerisations catalysed by the Chloroacetic Acids.*

By C. P. Brown and A. R. Mathieson.

The reactions of trichloroacetic acid with various vinyl compounds have been investigated. Addition to form the trichloroacetate occurs with hydrocarbons containing unconjugated unsubstituted double bonds. Conjugation with other double bonds and the phenyl group leads to the formation of polymers of relatively low molecular weight. Strong electrophilic substituents inhibit both addition and polymerisation.

Most detailed studies of cationic polymerisations have been made with Friedel–Crafts catalysts, and the mechanisms by which they function are very complex (see, *e.g.*, Pepper [1]). Strong hydrogen acids such as sulphuric acid (Heiligmann [2]) and hydrochloric acid (Pepper and Somerfield [3]) catalyse the polymerisation of styrene and α-methylstyrene. Many other acids, including acetic, formic, phosphoric, hydrofluoric, nitric, trichloroacetic, sulphuric, and hydrochloric, bring about dimerisation and "conjunct" polymerisation as well as true polymerisation of a wide range of monomers, mostly alkenes, and most of the results are recorded in patents.[4]

Since these hydrogen acids contain readily available protons they may function in a simpler manner than the Friedel–Crafts halides. Also, certain series exist where the acid strength changes in a known, regular way. Such a series is the three chloroacetic acids, a comparison of whose catalytic activities for the same monomer might yield valuable information on the mechanism of the reaction. Furthermore, the fate of an acid catalyst during polymerisation is much more readily determined than that of a Friedel–Crafts halide.

Trichloroacetic acid has been used to convert buta-1 : 3-diene homologues into rubbers [5] and to form dimers and polymers of *cyclo*pentadiene.[6] The chloroacetic acids also co-catalyse Friedel–Crafts polymerisations of *iso*butene; trichloroacetic and dichloroacetic acids titanium tetrachloride-catalysed polymerisation [7] and acetic acid boron trifluoride-catalysed polymerisation.[8] Trichloroacetic acid co-catalyses the titanium tetrachloride-catalysed polymerisation of styrene [9] and stilbene.[10] Russell [11] compared the effect of different co-catalysts on the polymerisation of *iso*butene by stannic chloride in ethyl chloride at −78° and found they are effective in the order $CCl_3{\cdot}CO_2H > Cl{\cdot}CH_2{\cdot}CO_2H \gg Me{\cdot}CO_2H > EtNO_2 > MeNO_2 > PhOH > H_2O$.

Results and Discussion

Reactions of the Chloroacetic Acids at Carbon–Carbon Double Bonds.—The mechanism of polymerisations catalysed by chloroacetic acids can be more readily understood against

* Part V, *J.*, 1952, 2363.

[1] Pepper, *Quart. Rev.*, 1954, **8**, 88.
[2] Heiligmann, *J. Polymer Sci.*, 1951, **6**, 155.
[3] Pepper and Somerfield, "Cationic Polymerisation," Heffer, Cambridge, 1953, p. 75; *Chem. and Ind.*, 1954, 42.
[4] *Chem. Abs.*, 1910, **4**, 1909; 1911, **5**, 3519; 1916, **10**, 47; 1920, **14**, 2480; 1927, **21**, 1444; 1928, **22**, 4281; 1930, **24**, 2423; 1932, **26**, 3406; 1933, **27**, 1638, 2572, 2591; 1934, **28**, 4587; 1935, **29**, 526, 1905, 5540.
[5] G.P. 542,647/1930; *Chem. Abs.*, 1932, **26**, 3406.
[6] Eisler, Wassermann, Farnsworth, Kendrick, and Schnurmann, *Nature*, 1951, **168**, 459; Eisler, Farnsworth, Kendrick, Schnurmann, and Wassermann, *J. Polymer Sci.*, 1952, **8**, 157.
[7] Plesch, *Nature*, 1947, **160**, 868.
[8] Evans, Meadows, and Polanyi, *Nature*, 1947, **160**, 869.
[9] Plesch, "Cationic Polymerisation," Heffer, Cambridge, 1953, p. 103.
[10] Brackman and Plesch, *ibid.*, p. 19.
[11] Russell, *ibid.*, p. 114.

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the background of the general reactions of these acids with carbon–carbon double bonds. Frequently trichloroacetic acid adds to a double bond,[12–15] rather than polymerising the olefin.

Since the action of the chloroacetic acids on only a few unsaturated compounds has been recorded, we have made a general survey of the effect of these acids on carbon–carbon double bonds. Unsaturated compounds were divided arbitrarily into five groups: (1) hydrocarbons containing "isolated" double bonds; (2) hydrocarbons containing conjugated double bonds; (3) compounds containing phenyl groups and double bonds; (4) compounds containing alkoxyl and carboxyl groups and double bonds; (5) compounds containing heterocyclic oxygen or nitrogen (see Table).

Trichloroacetic acid was added at 20° to the olefin either pure or, if reaction was slow, in ethylene dichloride or nitromethane. Up to 20% of the acid was added if necessary to

Summary of reactions of trichloroacetic acid at double bonds.

Class	Compound	Reaction *	Polymer D.P.	Polymer C (%)	Polymer H (%)	Polymer Cl (%)
1	3-Methylbut-2-ene	Addn.				
	Pent-2-ene	,,				
	*cyclo*Hexene	,,				
	Pinene	,,				
	Limonene	,,				
2	Isoprene	Conj. Polyn.	5—6	66·2	8·41	17·9
	Phellandrene	Polyn.	9—10	78·1	9·42	7·48
	*cyclo*Pentadiene	,,	18			
3	Styrene	Polyn.	10—20			3·25—9·51
	p-Chlorostyrene	,,				
	α-Methylstyrene	,,	2—15			6·7—24·8
	Anethole	,,	9—10			
	*iso*Safrole	,,	?			nil
	*iso*Eugenol	,,	?			nil
	Indene	,,	20			nil
	Safrole	None				
	Eugenol	,,				
	Stilbene	,,				
4	*n*-Butyl vinyl ether	A(P)				
	Ethyl vinyl ether	,,				
	2-Chloroethyl vinyl ether	,,				
	Phenyl vinyl ether	,,	7—9	64·6	7·35	9·86
	Methyl acrylate	None				
	Ethyl acrylate	,,				
	Methyl methacrylate	,,				
	Coumarin	,,				
	Cinnamic acid	,,				
5	2 : 3-Dihydropyran	Polyn.	7—8			18·3
	Pyrrole	,,		Insoluble resin		
	Coumaranone	,,				
	Indole	,,	2—3	N, 8·6		26·4
	β-Methylindole	None				

* Addn., Addition; Polyn., Polymerisation; A(P) Addition with a little polymerisation.
? Not certain.

achieve a positive result. Several methods were used conjointly to determine, when reaction occurred, whether it was addition or polymerisation or both, namely, observation of change of temperature and increase in viscosity, alcohol precipitation of polymers, acid titration, titration of residual double bonds, and microchemical analysis and molecular weights of products. The results are summarised in the Table.

[11] Scovill, Burk, and Herman, *J. Amer. Chem. Soc.*, 1944, **66**, 1039.
[13] Nernst and Hohmann, *Z. phys. Chem.*, 1893, **11**, 352.
[14] Timotheev, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 838.
[15] Dorris, Sowa, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2689.

The reactions of trichloroacetic acid at isolated double bonds are similar to those of the hydrogen halides, addition generally taking place in accordance with Markownikov's rule, *e.g.*, with 3-methylbut-2-ene:

$$Me_2C = CHMe + CCl_3{\cdot}CO_2H \longrightarrow CCl_3{\cdot}CO_2{\cdot}CMe_2{\cdot}CH_2Me$$

These addition products tend to be unstable, and with water yield the alcohol in some cases even at room temperature. For instance, the reaction

$$MeHC = CHEt + CCl_3{\cdot}CO_2H \longrightarrow CCl_3{\cdot}CO_2{\cdot}CHMe{\cdot}CH_2Et$$

is endothermic and on addition of water evolution of heat is accompanied by the formation of the corresponding alcohol, $HO{\cdot}CHMe{\cdot}CH_2Et$. The product of dimerisation of α-methylstyrene with trichloroacetic acid loses the acid radical similarly, and this is reasonably true for all the polymers.

With compounds containing conjugated double bonds both addition and polymerisation can occur. With isoprene, both proceed simultaneously; in absence of solvent about 10% of the isoprene is polymerised; in nitromethane the reaction is very rapid and more polymer is formed (20—30%). Phellandrene in absence of solvent is over 90% polymerised. The chlorine content of these two polymers indicates that there is one trichloroacetate end-group per polymer molecule.

Styrene and α-methylstyrene are readily and quantitatively polymerised by trichloroacetic acid in the absence of solvent and in solution; α-methylstyrene yields a large proportion of dimer. Both polymers contain one trichloroacetate group per polymer molecule. Anethole gives mainly the dimer in absence of solvent but polymers of D.P. 9—10 in ethylene dichloride. *iso*Eugenol and *iso*safrole react readily in ethylene dichloride, giving polymers containing a chlorine-free fraction insoluble in ethylene dichloride, benzene, or ether, and a soluble fraction of molecular weight 1000—1200. Solutions of eugenol and safrole become bottle-green in the presence of trichloroacetic acid but no reaction can be detected. An approximate study of the relative rates of polymerisation in this class of monomer showed the sequence anethole > α-methylstyrene > *iso*eugenol = *iso*safrole > styrene. Indene yields a chlorine-free high polymer with trichloroacetic acid, both without solvent and in ethylene dichloride.

The chloroacetic acids react exothermically with the alkyl vinyl ethers, but very little polymer is formed. The product from butyl vinyl ether has a molecular weight of 203 (Found: C, 65·5; H, 12·8%) and contains only a trace of chlorine. It is probably largely butyl alcohol with condensation products and a trace of polymer. Phenyl vinyl ether in nitromethane reacts readily with trichloroacetic acid giving 10—15% of polymerisation, the remainder undergoing the alternative reaction. The acrylates are more readily polymerised by anionic catalysts and it is not surprising that the chloroacetic acids are without effect. No reaction was detected even when the monomer was kept in dichloroacetic acid for several days. Pfeiffer *et al.*[16] have described an addition compound between trichloroacetic acid and cinnamic acid.

2 : 3-Dihydropyran is readily polymerised by trichloroacetic acid and the polymers contain one trichloroacetate group per polymer molecule. An insoluble polymer is obtained from pyrrole with trichloroacetic acid. Indole gives a polymer which is more readily soluble in alcohol than in benzene, ether, or acetone. Both the poly-2 : 3-dihydropyran and the polyindole contain one trichloroacetate end-group per polymer molecule.

Conclusions.—It is clear that, for polymerisation to occur, there must be some degree of resonance between the double bond and other double bonds or a phenyl group. Addition occurs readily with unsubstituted isolated double bonds (class 1), conjugation leads to polymerisation together with addition (isoprene), and resonance with a phenyl group leads to polymerisation alone (class 3). Comparison of eugenol and safrole with *iso*eugenol and *iso*safrole is interesting; in eugenol and safrole resonance with the phenyl

[16] Pfeiffer, *Ber.*, 1914, **47**, 1580.

group is prevented by the insertion of a methylene group between the double bond and the phenyl group, and no polymerisation takes place. Steric hindrance may be responsible for the inability of these catalysts to polymerise stilbene. Strongly electronegative groups on the carbon atoms of the ethylenic double bond tend to deactivate it towards both addition and polymerisation. Where the double bond is adjacent to an ether linkage reaction with the oxygen atom predominates, but again the presence of a phenyl group enhances polymerisation. The cyclic compounds of this type show a greater tendency to polymerise.

The Polymers.—The polymers formed can be divided into two groups, with or without trichloroacetate end-groups; in the former there is always one end-group per polymer molecule. The interpretation of the chlorine content of the polymers in terms of trichloroacetate end-groups has been justified, for styrene and α-methylstyrene, by infrared analysis and a test for ester-linkages.[17] This difference in the constitution of the polymers suggests a significant difference in the mechanism of their formation; styrene and indene could be representative of either class and so the kinetics and mechanism of the polymerisation of both compounds were investigated in detail. The results for styrene and α-methylstyrene are reported in the following papers.

Experimental

Materials.—The chloroacetic acids were recrystallised from benzene and fractionated at reduced pressure, the middle fraction of constant b. p. being retained. They were then distilled from $MgSO_4$ to remove water and stored in an atmosphere of dry nitrogen. Styrene and α-methylstyrene were shaken with aqueous potassium hydroxide, washed with water, and fractionated thrice under reduced pressure. After a final distillation from barium monoxide to remove water they were stored in the dark in an atmosphere of dry nitrogen. The other vinyl compounds were washed with aqueous sodium hydroxide and water, then fractionated under reduced pressure. They were distilled from calcium chloride to remove water and stored under dry nitrogen. Nitromethane was refluxed for several hours in a current of dry nitrogen, then fractionated from calcium chloride. Ethylene dichloride was washed with aqueous sodium hydroxide, then water, and fractionated from calcium chloride.

Extraction of Polymers.—Polymers insoluble in methanol were dissolved in benzene, reprecipitated, and redissolved. The solution was frozen as a film inside a tube with solid CO_2–methanol, and the tube was evacuated for several hours to remove all remaining monomer and solvent. This process was repeated to constant weight. Polymers soluble in methanol were extracted by shaking the solution several times with water to remove excess of catalyst and evaporating the solution under reduced pressure at room temperature to remove most of the solvent and unchanged monomer. The extract, consisting of polymer of low molecular weight contaminated with solvent and unchanged monomer, was subjected to a horizontal temperature gradient for several hours, whereupon the various fractions collected along different sections of the evacuated tube.

Titration of Residual Monomer and Acid.—Solutions of 0·1—0·2N-bromine in glacial acetic acid were added to known amounts of the reaction solution and excess of bromine was estimated with potassium iodide and thiosulphate. To estimate acid, known fractions of the solutions were extracted with water, and excess of sodium hydroxide was added and back-titrated with hydrochloric acid. This was not possible for nitromethane solutions.

Viscosities.—Ostwald viscometers were used.

Molecular Weights.—These were determined cryoscopically in benzene by the Beckmann method.

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The University, Nottingham.
[Present Address (A. R. M.).—University College, Ibadan, Nigeria.]

[*Received, December 10th,* 1956.]

[17] Brown and Mathieson, *J.*, 1957, 3620.

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716. *The Kinetics of Catalytic Polymerisations. Part VII.* Kinetics of the Polymerisation of Styrene catalysed by Di- and Tri-chloroacetic Acid.*

By C. P. Brown and A. R. Mathieson.

The kinetics of the ionic polymerisation of styrene catalysed by di- and tri-chloroacetic acid have been investigated. The dependence of the rates on monomer [M] and catalyst [C] concentrations is given by $-d[M]/dt = k_0[M]^2[C]^{3\cdot5}$ for the reaction in absence of solvent, $-d[M]/dt = k_0[M]^2[C]^2$ for ethylene dichloride solutions, and $-d[M]/dt = k_0[M]^2[C]$ for nitromethane solutions. Polymerisation does not occur in the complete absence of water and solvent, and in absence of solvent the rate is proportional to water concentration when this is small. The acid catalysts are consumed during the reactions at abnormally high rates. The overall energies of activation lie between 3 and 14 kcal. mole^{-1}, being greater the more rapid the reaction. Increase of the dielectric constant (D) of the medium increases the reaction rate according to $-d[Me]/dt = Ke^{-\alpha D}$ (K and α are constants). The molecular weights of the polymer lie between 700 and 2300 at 25°, and increase linearly with monomer and with catalyst concentrations. Increased dielectric constant causes increased molecular weight, such that log $M \propto (D - 1)/(2D + 1)$ and log $1/M$ decreases linearly with $1/T$. *p*-Benzoquinone (Q) retards the polymerisations, the rate becoming proportional to $[Q]^{-\frac{1}{2}}$, and it also reduces the molecular weights of the polymer. The quinone is converted into the red ion QH_2^{2+} and finally into quinhydrone; a mechanism for this inhibition is formulated. Acetone, nitrobenzene, and 1 : 3 : 5-trinitrobenzene inhibit the polymerisation.

Chloroacetic acids are very much weaker polymerisation catalysts than the metal halides. Nevertheless, in the presence of di- or tri-chloroacetic acid, styrene is converted quantitatively into a white polymer at room temperature. The rates of these reactions are linear frequently up to as much as 30% polymerisation. Trichloroacetic acid is a stronger catalyst than dichloroacetic acid, and monochloroacetic acid does not polymerise styrene under normal conditions, though it will polymerise the somewhat more reactive α-methylstyrene. These reactions occur much more rapidly in media of high dielectric constant, such as nitromethane or ethylene dichloride, than in benzene or without solvent. Quinones and nitro-compounds retard, but do not completely inhibit, the polymerisations and their use results in polymers of lower molecular weight. In the complete absence of solvent and water there is no reaction. Lowering the temperature markedly decreases the reaction rates and the polymers are then of greater molecular weight.

The rates are extremely sensitive to the reactant concentrations and this, together with the weakness of the catalysts, makes it necessary to study the reactions at catalyst concentrations higher than would otherwise be desirable. Hence the catalyst solutions cannot be treated as ideal when the kinetics are being interpreted in terms of mechanisms. We now report the influences of reactant concentration, water, retarders, temperature, and dielectric constant on the rate of the polymerisation of styrene catalysed by di- and tri-chloroacetic acid and on the constitution of the polystyrene formed. Some of these results have already been summarised.[1]

Results and Discussion

Quantitative Nature of the Polymerisations.—For a detailed kinetic analysis it must be established that the conversion of monomer into polymer is quantitative and that no

* Part VI, preceding paper.

[1] Brown and Mathieson, *Ricerca sci.*, 1955, **25**, Sup. Simp. Int. Chim. Macromol.

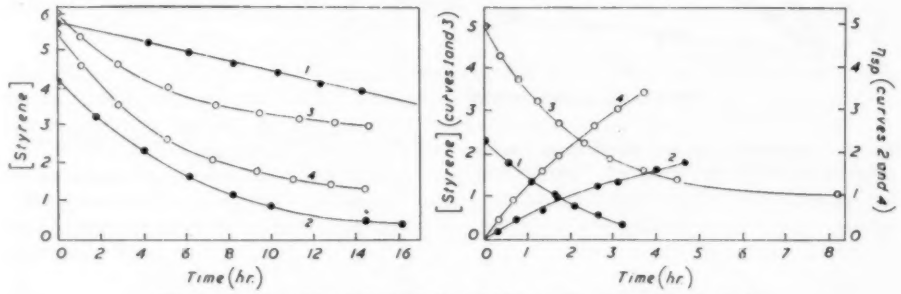
monomer is consumed in side reactions. Solutions of known concentrations of styrene and trichloroacetic acid in ethylene dichloride were allowed to react to given degrees of monomer conversion, and the quantities of polymer formed were measured. The results (Table 1) indicate that the polymerisation is fully quantitative, the agreement between the experimental amounts of polymers obtained and those calculated on the assumption of quantitative polymerisation being within experimental error.

TABLE 1. *Quantitative monomer polymerisation*

Initial monomer concn. (moles l.$^{-1}$)	1·36	1·36	1·97	2·63
Monomer conversion (%)	97·4	97·4	56·7	83·4
Wt. of monomer converted per 100 g. of solution	13·81	13·81	11·63	22·85
Wt. of polymer obtained per 100 g. of solution	13·68	13·95	11·58	23·10

Rates of the Polymerisations in the Pure Monomer.—Typical reaction–time curves are shown in Figs. 1 and 2. The reproducibility of the reaction rates is illustrated in Fig. 3,

FIGS. 1 and 2. *Typical reaction–time curves for the bulk polymerisation.*



Dichloroacetic acid catalysis, 1, 2; trichloroacetic acid catalysis, 3, 4.

and is clearly of a high order, particularly in the slower reactions. Table 2 shows the initial reaction rates for different reactant concentrations.

TABLE 2. *Dependence of initial rates (moles l.$^{-1}$ sec.$^{-1}$) of the polymerisation on initial concentrations (no solvent).*

Dichloroacetic acid						
[M]	4·20	4·40	4·60	5·00	5·30	5·80
[C]	4·90	4·50	4·10	3·80	3·60	3·00
$10^6 \times$ Rate	13·7	9·50	7·50	6·50	6·18	2·92
Trichloroacetic acid						
[M]	4·90	5·20	5·30	5·60	5·80	6·00
[C]	3·90	3·60	3·20	2·50	2·10	1·70
$10^4 \times$ Rate	2·85	2·32	1·52	0·518	0·367	0·157

Since the rates of polymerisation depend on the water concentration when this is below a certain value, the reactions were carried out at a constant concentration of water of 0·70 mole l.$^{-1}$. Above 0·60 mole l.$^{-1}$ of water the rates are of zero order with respect to the water concentration.

The dependence of the initial rate of polymerisation, for both di- and tri-chloroacetic acid catalysis, is given by

$$-d[M]/dt = k_o[M]^2[C]^{3.5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where [M] and [C] are the *initial* concentrations of monomer and catalyst respectively and k_o is the overall rate constant. At 25° k_o is $7{\cdot}3 \times 10^{-3}$ for dichloroacetic acid and

$3{\cdot}1 \times 10^{-6}$ for trichloroacetic acid, and so the relative rates for the two acids are **1 : 43**. The acid dissociation constants are in the ratio **1 : 24**.

In the complete absence of water and solvent dichloroacetic acid does not catalyse the polymerisation of styrene, so that water is a cocatalyst for this reaction. Fig. 4 shows the way in which the reaction rate is influenced by the water concentration. At low concentrations of water the rate is directly proportional to it, but at higher concentrations

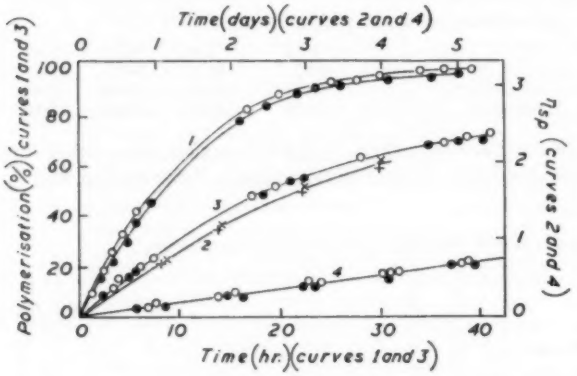


FIG. 3. *Reproducibility of the bulk polymerisation.*

Trichloroacetic acid catalysis, **1**, **2**; dichloroacetic acid catalysis **3**, **4**.

FIG. 4. *Dependence of the dichloroacetic acid-catalysed polymerisation upon water concentration.*

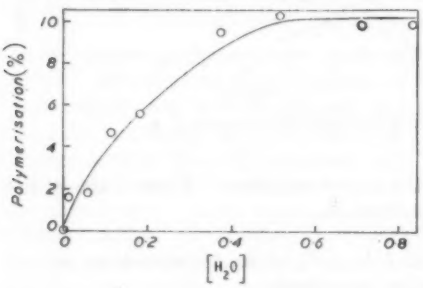
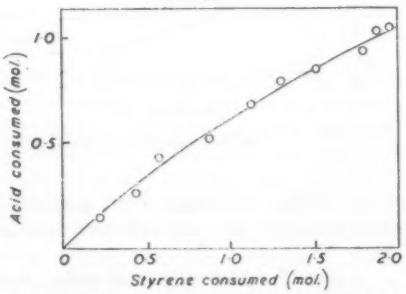


FIG. 5. *Consumption of the dichloroacetic acid catalyst.*



Initial molar concns.; acid 1·7, styrene 6·1.

of water the rate becomes independent of it. Still higher concentrations of water (not shown in Fig. 4) reduce the rate. At low water concentrations the initial rate obeys

$$-\mathrm{d[M]/d}t = k_o'[\mathrm{M}]^2[\mathrm{C}]^{3\cdot5}[\mathrm{H_2O}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The acid catalysts are consumed during polymerisation, as can be demonstrated by direct titration during the reaction as well as by incorporation of catalyst in the polymer. Plots of residual monomer and catalyst concentrations during reaction show a rapid consumption of catalyst compared with that of monomer in the initial stages of the reaction. For dichloroacetic acid the mole ratio (acid consumed) : (monomer consumed) is as low as 0·5 for the first 10% of the reaction. The ratio falls as reaction proceeds, reaching 1 : 15 at 90—100% polymerisation. A typical plot of acid consumed against monomer consumed is shown in Fig. 5 for the initial stages of a reaction, and Table 3 shows values for both di- and tri-chloroacetic acid catalysis. For trichloroacetic acid the ratio never falls much below 0·5, and this suggests extensive formation of monomer–catalyst or polymer–catalyst complex.

Rates of the Polymerisations in Ethylene Dichloride.—It was not possible to influence the rate of polymerisation by decreasing the water concentration to very low values for

TABLE 3. *Relative rates of consumption of monomer and catalyst (catalyst consumed per mol. of monomer consumed).*

Monomer conversion (%)	10	20	30	50	100
Dichloroacetic acid (mol.)	0·498	0·283	0·200	0·121	0·0641
Trichloroacetic acid (mol.)	1·19	0·953	0·885	0·552	0·449

TABLE 4. *Dependence of initial rates (moles $l.^{-1}$ $sec.^{-1}$) of the polymerisation in ethylene dichloride on initial concentrations at 25°.*

Dichloroacetic acid						Trichloroacetic acid					
[M]	2·00	2·08	2·18	3·50	4·72	[M]	1·44	1·48	1·70	1·78	1·89
[C]	2·20	4·28	3·32	3·00	2·56	[C]	1·80	0·84	1·60	1·00	1·30
$10^4 \times$ Rate	0·917	4·17	2·78	5·78	7·62	$10^4 \times$ Rate	2·52	0·550	2·22	1·03	3·18

ethylene dichloride solutions. It may be that the increased dielectric capacity of the medium favours the autoprotolysis of the catalyst, or that the solvent can act as a co-catalyst. At fairly large water concentrations the rate decreased steadily on increase of water concentration. The dependence of the rate of polymerisation on the reactant concentrations is shown in Table 4. For both acids the kinetics of the reactions are accurately described by

$$-d[M]/dt = k_o[M]^2[C]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The values of k_o are $3{\cdot}12 \times 10^{-5}$ for dichloroacetic and $1{\cdot}85 \times 10^{-3}$ for trichloroacetic acid, the rates being in the ratio 1 : 59. The change in the dependence of the rate upon catalyst concentration on introduction of ethylene dichloride into the systems is most striking.

The catalysts are again consumed during reaction, and Table 5 shows the relative rate of consumption of monomer and catalyst for both acids. In both cases the mole ratio (acid consumed) : (monomer consumed) increases steadily throughout the reaction, for trichloroacetic acid the ratio being again much higher and subject to a much smaller increase.

TABLE 5. *Relative rates of consumption of monomer and catalyst in ethylene dichloride (catalyst consumed per mol. of monomer consumed).*

Monomer conversion (%)	10	20	30	50	100
Dichloroacetic acid (mol.)	0·316	0·213	0·160	0·133	0·0978
Trichloroacetic acid (mol.)	0·424	0·411	0·408	0·389	0·318

Rates of the Polymerisations in Nitromethane.—The reactions are more rapid in nitromethane, and Table 6 shows the results for di- and tri-chloroacetic acid catalysis. Eqn. (4) accurately described the kinetics :

$$-d[M]/dt = k_o[M]^2[C] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The values of the overall rate constant are $k_o = 1{\cdot}6 \times 10^{-4}$ for dichloroacetic and $7{\cdot}3 \times 10^{-3}$ for trichloroacetic acid, the relative rates being 1 : 46. The consumption of the acid catalyst cannot be investigated in nitromethane by the method used for polymerisations without solvent and in ethylene dichloride.

TABLE 6. *Dependence of initial rates (moles $l.^{-1}$ $sec.^{-1}$) of the polymerisation in nitromethane on initial concentrations at 25°.*

Dichloroacetic acid						Trichloroacetic acid					
[M]	1·03	1·17	1·32	1·42	1·59	[M]	1·70	1·93	2·00	2·95	3·13
[C]	2·01	2·10	1·98	2·11	1·98	[C]	1·01	1·60	1·21	1·29	1·02
$10^4 \times$ Rate	3·33	6·82	9·17	12·2	14·3	$10^4 \times$ Rate...	1·00	3·00	2·00	5·50	4·33

The reaction rate decreases with increased concentration of water, and in this solvent the conductance of the reactant solution has been measured for different water concentrations at constant monomer and acid concentration. The results (Table 7) show that increase in water concentration increases the conductance but decreases the rate of

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TABLE 7. *Conductance of reactant solutions at 25°.*

(Monomer concn. = 1·61, catalyst concn. = 2·11 moles l.$^{-1}$.)

Water concn. (moles l.$^{-1}$)	~0	0·15	0·36	0·78	1·01	2·37
Equivalent conductance (ohm^{-1} cm.$^{-1}$) ...	~0	0·0793	0·168	0·301	0·497	1·26
10^3 Reaction rate (moles l.$^{-1}$ sec.$^{-1}$)	1·45	1·42	1·33	1·18	1·50	0·60

polymerisation. The presence of a measurable concentration of hydrogen ion does not appear to increase the reaction rate. It may be that competition occurs between the water and the monomer for the proton of the acid, or alternatively that the ionisation step is not rate-determining.

Temperature-dependence of the Reaction Rates.—Polymerisations catalysed by both di- and tri-chloroacetic acid were performed without and with solvents at 0°, 25°, and 40°. Agreement with the Arrhenius equation was found in all cases. Values of the overall energy of activation (E_o) for the reactions were calculated from the results and these are shown in Table 8.

TABLE 8. *Overall energy of activation (kcal. mole^{-1}).*

Solvent	Styrene	C_2H_5Br	$C_2H_4Cl_2$	$C_2H_5{\cdot}NO_2$	$CH_3{\cdot}NO_2$
Dielectric constant	2·0	4·87	10·5	19·7	39
E_o, Dichloroacetic acid	5·5	3·0	6·0	—	8·0
E_o, Trichloroacetic acid	9·0	3·0	8·0	10·0	14·0

It is significant that, if polymerisations without solvent are not counted, the energy of activation increases with increasing dielectric constant of the solvent. Increased dielectric constant also increases the rate of the reaction and the apparent anomaly exists that the reactions proceed the more rapidly the greater the energy of activation. This has been noticed for ionic polymerisations before,[2] values of E_o of 10·0 and 15·0 kcal. mole^{-1} being obtained for the polymerisation of octyl vinyl ether catalysed by iodine in hexane and ethylene respectively. Also, for the polymerisation of styrene catalysed by stannic chloride,[3] it was found that $E_o = 3{\cdot}0$ kcal. mole^{-1} for carbon tetrachloride solutions, and $E_o = 4{\cdot}5$ kcal. mole^{-1} for ethyl chloride solutions.[4] An interpretation of this effect in terms of complex-formation between monomer and catalyst will be given in Part X.

Variation of the Reaction Rates with the Dielectric Constant of the Medium.—The relatively large concentrations of monomer and catalyst employed make it essential to measure the dielectric constant of the reaction solutions, since it cannot be assumed to be equal to that of the solvent. The rates of the polymerisation of styrene catalysed by trichloroacetic acid in a series of benzene–nitromethane mixtures and in a series of benzene–ethylene dichloride mixtures were measured viscosimetrically, and can be compared for experiments at the same monomer and catalyst concentrations by comparing the values of the specific viscosity (η_{sp}) of the solutions after the same short time interval, during the initial period of the reaction when η_{sp} is a linear function of time. Fig. 6 shows these results, from which

$$-\mathrm{d[M]}/\mathrm{d}t = Ke^{-\alpha D} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where K and α are constants for all mixtures of the same two solvents.

Various equations connecting the rate of chemical reaction with the dielectric constant of the medium have been suggested.[7]

$$\ln k = B + C(D-1)/(2D+1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$\ln k = B + C(1/D-1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Neither of these expressions agrees with our results [eqn. (5)].

[2] Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 425, 436.
[3] Williams, *J.*, 1938, 246, 1046.
[4] Gantmaker and Medvedev, *Zhur. fiz. Khim.*, 1949, **23**, 516.
[5] Glasstone, Laidler, and Eyring, "Theory of Rate Processes," McGraw-Hill, New York, 1945, p. 419.
[6] Laidler and Eyring, *Ann. New York Acad. Sci.*, 1940, **39**, 303.
[7] Wassermann *et al.*, *Nature*, 1951, **168**, 459; *J. Polymer Sci.*, 1952, **8**, 157.

The increase in reaction rate with dielectric constant demonstrates the ionic nature of these polymerisations, and the magnitudes of the energies of activation and polymer molecular weights are also those to be expected for ionic polymerisations.

Molecular Weights of the Polymers.—The number-average molecular weights of the polymers, measured cryoscopically, were 700—2300, and depended on the reaction conditions, but showed slight variation between the two catalysts. In ethylene dichloride and in nitromethane, the molecular weight of the polymer varied with the extent of reaction and with the initial monomer concentration (Table 9) at constant trichloroacetic acid concentration. These results show that the molecular weight increases linearly with the monomer concentration. In ethylene dichloride the recorded molecular weight takes account of all the polymer formed up to the given degree of monomer conversion. For monomer concentrations between 1·0 and 5·0M the molecular weight (M) is given by

$$M = 1100 + 200[\mathrm{M}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and

$$M = 975 + 70[\mathrm{M}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

for nitromethane and ethylene dichloride solutions respectively.

TABLE 9. *Dependence of molecular weight on monomer concentration at* 25°.

	Nitromethane				Ethylene dichloride				
[M] (initial)	1·21	2·42	3·63	4·84	4·15	4·15	4·15	4·15	4·15
Conversion (%) ...	20·15	21·10	20·36	20·11	19·8	37·2	51·2	63·1	79·9
M	1300	1650	1850	2000	1250	1210	1190	1190	1150

TABLE 10. *Dependence of molecular weight on catalyst concentration at* 25°.

	Nitromethane				Ethylene dichloride			
[C]	1·20	2·40	3·60	4·80	0·70	1·80	3·30	5·00
M	1300	1600	1800	1950	1150	1300	1500	1700

The molecular weight also increases linearly with the catalyst concentration, and Table 10 shows this effect for trichloroacetic acid catalysis.

The dependence of molecular weight on catalyst concentration can be given as

$$M = 1000 + 190[\mathrm{C}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and

$$M = 1100 + 120[\mathrm{C}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

for nitromethane and ethylene dichloride respectively. Dependence of the molecular weight on catalyst concentration is unusual for ionic polymerisation, but has been observed for other systems catalysed by trichloroacetic acid.[7]

The influence of the dielectric constant of the medium on the molecular weight was studied by carrying out the reaction at constant concentrations of monomer and catalyst in different solvents. Table 11 shows that increased dielectric constant increases the

TABLE 11. *Dependence of molecular weight on dielectric constant at* 25°.

Solvent	*cyclo*Hexane	$C_2H_4Cl_2$	$C_2H_5{\cdot}NO_2$	$CH_3{\cdot}NO_2$
D	1·9	8·7	20	31
M (trichloroacetic acid)	800	970	1090	1160
M (dichoroacetic acid)	720	910	980	1050

molecular weight. The results obey an equation analogous to eqn. (6) with molecular weight substituted for reaction rate, *i.e.*,

$$\log M = B + C(D - 1)/(2D + 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

in which $C = 0{\cdot}23$ for both acids, and $B = 2{\cdot}85$ and 2·90 respectively for di- and trichloroacetic acid.

The variation of molecular weight with the temperature of reaction was studied over the range −80° to +40° with trichloroacetic acid and ethyl bromide as solvent. The

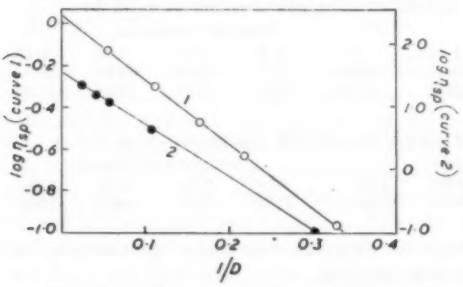
rate at −80° was so small that the solution had to be allowed to react for 6—8 weeks in a sealed tube in the dark for sufficient polymer to be formed. Values of $-\log 1/M$ for various values of $10^3/T$ (in parentheses) of 3·03(3·2), 3·10(3·7), and 3·37(5·4) show that $\log (1/M)$ decreases linearly with $1/T$. Since the chain length of the polymer (n) is given by the ratio of the rate of propagation to the rate of chain termination, *i.e.*, $n = V_p/V_t$, no chain-transfer being assumed, it follows for spontaneous termination that

$$\ln 1/n = \ln (k_t/k_p[M])(E_p - E_t)/RT \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where k_p, k_t, E_p, and E_t are the specific rates and activation energies of propagation and termination. The value of $E_p - E_t$ can be calculated from the results given above to be −850 cal. mole^{-1}.

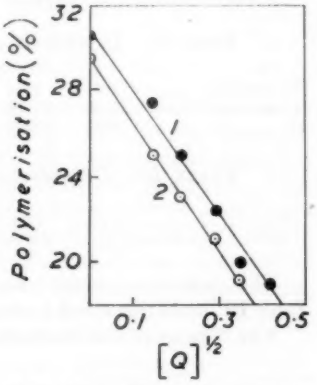
Effect of p-*Benzoquinone on the Polymerisations.*—Quinones retard the chloroacetic acid-catalysed polymerisations in spite of their ionic character, and 1M-quinone can

FIG. 6. *Effect of dielectric constant on reaction rate.*



I, Benzene–ethylene dichloride mixtures; II, benzene–nitromethane mixtures.

FIG. 7. *Effect of benzoquinone on the rate of polymerisation of styrene by trichloroacetic acid.*



I, Ethyl bromide solution, after 41 hr.; II, Bulk polymerisation, after 47 hr.

inhibit reaction completely. Lower concentrations retard rather than inhibit, and no induction periods can be observed. Dilute solutions of *p*-benzoquinone (Q) in either styrene or dichloroacetic acid are the normal yellow colour, but immediately on addition of the second reactant (either dichloroacetic acid or styrene) the solour changes to bright red which after several hours tends to become dark green. In concentrated solutions of quinone the appearance of the red colour is followed by an immediate darkening and the deposition of a dark green precipitate. The precipitate was shown by its m. p., molecular weight, and microchemical and *X*-ray powder analysis to be quinhydrone. The red colour was shown to be due to the QH_2^{2+} ion, first identified by Mackenzie and Winter,[8] by absorption spectroscopy.

The kinetics of the polymerisation were examined in the presence of different concentrations of benzoquinone, and Fig. 7 shows clearly that the rate of polymerisation is inversely proportional to the square root of its concentration, at constant concentrations of monomer and catalyst, *i.e.*, $-d[M]/dt = k[Q]^{-\frac{1}{2}}$. The molecular weight of the polymer formed at 20% monomer conversion in the presence of benzoquinone (moles l.$^{-1}$, in parentheses) is decreased in proportion to the amount of quinone present, as follows: 1200(0·00), 1100(0·01), 1060(0·05), 1000(0·10), 820(0·50), 530(1·10). All these results can be explained

[8] Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159.

by supposing that a benzoquinone molecule collides separately with two growing polymer ions (M_n^+):

$$M_n^+ + Q \longrightarrow M_n + QH^+$$
$$M_n^+ + QH^+ \longrightarrow M_n + QH_2^{2+}$$

this leads to the inverse-square-root dependence of the rate on quinone concentration, explains the chain-breaking action of the quinone in reducing the molecular weight, and allows for the formation of the observed ion QH_2^{2+}. To account for the formation of quinhydrone it is necessary to postulate the reaction

$$QH_2^{2+} + Q \longrightarrow Q_2H_2$$

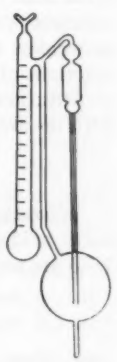
This mechanism of quinone inhibition is similar to that postulated for the inhibition by amines of the stannic chloride-catalysed polymerisation.[9] In that case the amine is supposed to form a stable ion M_n–NR_3^+. This retardation of an ionic polymerisation by quinone implies that quinone inhibition can no longer be taken as a criterion of a free-radical polymerisation.

Other Inhibitors and Retarders.—The polymerisation is completely inhibited by acetone, nitrobenzene, and 1 : 3 : 5-trinitrobenzene, and the formation of stable inhibitor–catalyst complexes is presumably responsible.

Experimental

Materials.—These were purified as in the preceding paper, and kept in sealed tubes or distilled, in dry nitrogen, into the reaction system. Ethyl bromide was treated with concentrated sulphuric acid to remove alcohol, washed with sodium carbonate solution and with water, and distilled from calcium chloride, the middle fraction being collected. Carbon tetrachloride was washed with alcoholic potassium hydroxide, then with water, and distilled from calcium chloride. "AnalaR" benzene was not further purified.

Fig. 8. *Vacuum viscometer.*



The Reaction System.—A high-vacuum glass apparatus was employed. Monomer, catalyst, and solvent were collected in separate sealed tubes, frozen, and the tubes joined to the vacuum system. The whole apparatus was thoroughly evacuated, and the monomer, catalyst, and solvent were separately distilled into a graduated chilled reaction vessel. The frozen reaction mixture was brought rapidly to the reaction temperature and the reaction mixture was run into a series of tubes, or into the vacuum viscometer, which were then sealed off and placed in a thermostat. The reaction was followed either by opening the sealed tubes at different times and titrating the mixture, or by measurement of viscosity. Fig. 8 shows a viscometer, specially designed for measurements under vacuum conditions. Viscometers of 10 and 20 ml. capacity were used.

To vary the water content of the reaction solution an evacuated bulb of approx. 1 l. capacity was allowed to attain the equilibrium water vapour pressure by connecting it to a smaller bulb containing water or ice at a known temperature. The large bulb was isolated and the vapour it contained was then condensed on the chilled reaction mixture.

Since the viscosity of a polymerising solution is a function of the polymer molecular weight as well as of the degree of monomer conversion, the viscosity was calibrated against the reaction rate determined by the sealed-tube method for each range of polymer molecular weight obtained.

The reaction solutions were analysed as in the preceding paper.

Dielectric Constant and Conductance Measurement.—A Marconi Universal bridge (1000 kc./sec.) with a range of 0·1 μμF to 1 F was used, in conjunction with a dielectric-constant cell consisting of three concentric brass tubes (9 cm. long, 2 cm. outside diameter) separated by mica strips, the inner and outer cylinders being joined by a brass strip. The conductance cell was of the standard form and had a cell constant of 0·4515.

[9] George, Mark, and Wechsler, *J. Amer. Chem. Soc.*, 1950, **72**, 3891; *J. Polymer Sci.*, 1951, **6**, 725.

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Molecular Weights of Polymers.—The polymers, extracted and purified as described in the preceding paper, were dissolved in benzene and the molecular weight measured cryoscopically at a series of polymer concentrations, the results being extrapolated to zero concentration.

THE UNIVERSITY, NOTTINGHAM.
[Present Address (A .R. M.).—UNIVERSITY COLLEGE, IBADAN, NIGERIA.]

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717. *The Kinetics of Catalytic Polymerisations. Part VIII.* The Constitution of Polystyrene formed by Di- and Tri-chloroacetic Acid Catalysis.*

By C. P. BROWN and A. R. MATHIESON.

The constitution of polystyrene formed by di- and tri-chloroacetic acid catalysis in different environments has been studied chemically and by infrared spectroscopy. Each polymer molecule contains a terminal chloroacetate group, which is lost above 70° and on alkaline hydrolysis. Polymers of low molecular weight lose this group more readily. No exchange of hydrogen between water and the acid catalysts occurs, and no fragments from the solvents nitromethane, ethylene dichloride, and butyl bromide are incorporated in the polymer. The polymer contains a very small amount of unsaturation. The relation between the molecular weight of the polymer M and its intrinsic viscosity $[\eta]$ in benzene solution is $[\eta] = 5{\cdot}2 \times 10^{-5}M$.

IN studies of the mechanism of polymerisations, knowledge of the exact constitution of the polymer generally permits certain definite conclusions to be drawn. It is at least as important as kinetic measurements, since these can sometimes be interpreted in terms of more than one reaction mechanism. It is possible for the same monomer, polymerised in different ways, to yield polymers of slightly different constitution. A knowledge of the molecular weight and the molecular-weight distribution, of certain simple chemical reactions of the polymer, and of the results of chemical and spectral analysis enables the constitution of the polymer to be completely described. Polystyrene prepared by catalysis with di- and tri-chloroacetic acid in various media has now been thus examined.

RESULTS AND DISCUSSION

Microchemical Analysis.—Polystyrene samples prepared by catalysis with trichloroacetic acid were analysed microchemically, and the results are shown in Table 1. Samples 1—5 are unfractionated polymers of normal molecular weight produced by polymerisation

TABLE 1. *Microchemical analysis.*

				Mol. wt.						Mol. wt.	
No.	C (%)	H (%)	Cl (%)	Obs.	Calc.	No.	C (%)	H (%)	Cl (%)	Obs.	Calc.
1	87·9	7·1	7·4	1100	1089	9	73·4	7·6	18·4	520	480
2	83·3	6·9	7·0	1300	1350	10	81·6	8·3	8·4	910	910
3	83·1	6·9	6·6	1310	1360	11	80·3	7·1	9·7	370	(950)
4	90·1	8·7	2·1	1550	1600	12	79·2	7·0	9·5	385	(950)
5	86·4	7·3	3·3	1850	1850	13	88·9	7·4	3·7	425	(2000)
6	59·5	5·2	24·6	260	280	14	81·4	8·7	9·5	475	(920)
7	59·2	5·5	24·3	270	275	15	86·4	7·4	3·3	520	(2500)
8	70·4	6·8	17·5	340	340						

in absence of solvent. Comparison of their molecular weights measured cryoscopically with the molecular weights calculated from the chlorine : carbon ratio by assuming that on average one catalyst molecule is incorporated in each polymer chain shows that this assumption is correct.

* Part VII, preceding paper.

More than one catalyst molecule might be incorporated per polymer molecule if some catalyst molecules lost chlorine atoms, but in view of the agreement of measured and calculated molecular weights and of the improbability of such loss under the experimental conditions, this possibility can be rejected. Samples 6—10 are polymers of low molecular weight obtained by fractionation by vacuum distillation below 30°. The agreement between their measured and calculated molecular weights confirms that one catalyst molecule is incorporated in each polymer chain. Since this is true for both unfractionated and fractionated polymers, the number of catalyst molecules incorporated per polymer molecule is not a function of molecular weight, but is unity for polymer molecules of all sizes.

Samples 11—15 are fractions of low molecular weight obtained by vacuum distillation above 70°. Here the calculated molecular weights are all too high, which shows that the incorporated catalyst is readily lost on distillation at these temperatures.

In Part VII it was shown that catalyst is consumed during polymerisation, and values of the mole ratio (acid consumed) : (monomer consumed) were given. This ratio for trichloroacetic acid is never greater than 1 : 3·14, so clearly only a part of this consumed acid can be accounted for by incorporation.

Analysis for Unsaturation.—Addition of bromine proved unsuitable, the uptake of bromine by the polymers continuing slowly for fairly long periods, and it is probable that some substitution in the phenyl rings or along the polymer chain took place. Micro-hydrogenation of the polymers at a palladium–charcoal catalyst, specific for ethylenic double bonds, was therefore employed. No unsaturation was found in any sample extracted by the normal procedure, but fractions of low molecular weight prepared by distillation above 70° were unsaturated. Table 2 describes the effect of repeated distil-

TABLE 2. *Effect of repeated distillation at 70° on the degree of unsaturation.*

Wt. of polymer (g.)	0·0319	0·0276	0·0298	0·0255	0·0317
No. of distilns.	0	1	2	3	4
Hydrogen uptake (moles × 10^5)	0	0·9298	1·945	2·738	3·537
Double bonds per molecule	0	0·16	0·31	0·51	0·53

lation at 70° on a mixture of polymers of initially an average molecular weight of 475. Together with the results in Table 1, which indicate a reduction of the chlorine content under the same conditions, these results show that at 70°, polymers of low molecular weight lose their incorporated catalyst, and a double bond is formed in its place. Polymers of higher molecular weight are stable at these temperatures, but the catalyst can be removed by alkaline hydrolysis, which suggests that the acid is incorporated as trichloroacetate end-groups. This is confirmed by a positive ester-linkages test for the polymers.

The Intrinsic Viscosity–Molecular Weight Relation.—The number-average molecular weights (M) of the polymer samples were determined cryoscopically in benzene, and the corresponding intrinsic viscosities ($[\eta] = \lim_{c \to 0} \eta_{sp}/c$) were measured [1] at 25° for benzene solutions. The plot of intrinsic viscosity against molecular weight is linear and passes through the origin; its equation is

$$[\eta] = 5{\cdot}2 \times 10^{-5} M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This relation differs from those of Staudinger [2] and Jordan and Mathieson,[3] who found $[\eta] = 1{\cdot}81 \times 10^{-5} M + 0{\cdot}0115$ for polystyrene of low molecular weight prepared by aluminium chloride catalysis. Kemp and Peters [4] however found that eqn. (1) held for unfractionated polymers. The trichloroacetate end-group, which is relatively large, could lead to increased viscosities.

[1] Fitzgerald and Fuoss, *Ind. Eng. Chem.*, 1950, **42**, 1603.
[2] Staudinger, " Die Hochmolekularen Organischen Verbindungen," Springer, Berlin, 1932.
[3] Jordan and Mathieson, *J.*, 1952, 611.
[4] Kemp and Peters, *Ind. Eng. Chem.*, 1942, **34**, 1097.

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TABLE 3. *Infrared spectra of benzyl esters (cm.$^{-1}$).*

Benzyl dichloroacetate	695 *	744	816 *	911	969	1000 *	1032	1165 *	1215
Benzyl trichloroacetate	680 *	759	828 *	893	969	1002		1159 *	1229 *
Benzyl dichloroacetate	1247 *	1280 *	1299	1375	1450	1499	1595	1760 *	
Benzyl trichloroacetate				1375	1450	1490	1595	1760 *	

Infrared Spectroscopy.—The infrared spectra were measured of a series of polystyrenes prepared under different conditions, and of benzyl dichloroacetate and benzyl trichloroacetate for comparison (Table 3). The polystyrene samples were examined as films 0·05 mm. thick prepared by evaporation of benzene solutions. The spectra of the polystyrenes are given in Table 4. Samples 1 and 2 are polystyrenes prepared by polymerisation without solvent by use of trichloroacetic acid and dichloroacetic acid as catalysts, respectively; samples 4 and 5 are fractions of low molecular weight (<800) of these polymers, respectively. Sample 9 was prepared by trichloroacetic acid catalysis without solvent, and then hydrolysed to remove trichloroacetate groups. Sample 11 was prepared by dichloroacetic acid catalysis without solvent in the presence of deuterium oxide (no H_2O). Sample 13 was prepared as sample 2, but is of higher molecular weight. Samples 16, 17, and 18 were prepared by dichloroacetic acid catalysis in ethylene dichloride, nitromethane, and *n*-butyl bromide solution respectively. Comparison of 1 and 2, and of 4 and 5 shows the influence of the two different catalysts; of 1 and 4 and of 2, 5, and 13 the influence of polymer molecular weight; of 1 and 9 the presence of catalyst fragments; of 1 and 11 the influence of water; and of 13, 16, 17, and 18 the rôle of the solvent.

TABLE 4. *Infrared spectra of polystyrene prepared by chloroacetic acid catalysis (cm.$^{-1}$).*

Sample nos.									
1	2	4	5	9	11	13	16	17	18
680m	680m	680m		680s	680s	680s	680s	680s	680s
700s	700s	700s	700s	742s	700s	700s	700s	700s	700s
762s	762s	750m	760m	760s	760s	760s	760m	760s	760s
830s	828w	760s	816m	800w	818m	830s	800w	820m	810s
885m	850w	845w	870w	844w	844m	860m	823w	843w	860m
917w	910w	910w	910w	870w	909m	880m	880w	875w	890m
965m	965w	940w	955m	909w	967m	925m	930m	900w	925m
983m	983w	960w	983m	938w	1015m	945m	985m	925w	945m
1005m	1020m	1005m	995m	967w	1035m	965m	1035m	947m	960m
1015m	1045m	1045m	1010m	980w	1070m	978m	1064w	995w	980m
1045s	1070w	1145w	1037m	1030m	1170m	998m	1160m	1030m	1005m
1180s	1180m	1175w	1057m	1070m	1283m	1035m	1225m	1070w	1035m
1215s	1215m	1235w	1077m	1110w	1376m	1060w	1235s	1090w	1060m
1255s	1240w	1255w	1155s	1150w	1441s	1110m	1278s	1140w	1110w
1290s	1280m	1290w	1200m	1176w	1474s	1135m	1290w	1180w	1135w
1350m	1455s	1350w	1230m	1250w	1555w	1195m	1310w	1240s	1195s
1390w	1470m	1445s	1268s	1303w	1770m	1235s	1360w	1278m	1225m
1470s	1485s	1460m	1325m	1323w	1800m	1278m	1470s	1310w	1278m
1515m	1555w	1475s	1435m	1376m	1880w	1310w	1500m	1360m	1310w
1600w	1585m	1525w	1475m	1450s	1930w	1360m	1560w	1470s	1360m
1635w	1770m	1565m	1590w	1470m	1980w	1470s	1600m	1500m	1470s
1740w	1800w	1585w	1620w	1485s	2520s	1500m	1760s	1560w	1500m
1760s	1880w	1760m	1680w	1615m	2940s	1560w		1600m	1560w
1930w	1930w	1880w	1760s	1670w		1600m		1760s	1600s
2520m	2520s	1930w	1860w	1760w		1760s			1760s
2940m	2940m	1980w	1930w	1880w					
3190w		2710m	2530m	1930w					
		2940s	2940m	1980w					
		3190m	3190m	2710m					
			3330w	2940s					
				3190m					
				3350w					

Examination for Catalyst Fragments and Unsaturation.—In Table 3 bands characteristic of the chloroacetate groups are marked by asterisks. Substitution of chlorine for hydrogen causes small shifts in the bands. Comparison of any of the polystyrene spectra in Table 4

(except no. 9) with the spectrum of polystyrene prepared by a free-radical mechanism shows clearly the presence of di- or tri-chloroacetate groups. For example, no. 5, which contained 24·6% of Cl, shows no new bands in the regions 1610—1550, 1420—1300, or 2500—2700 cm.$^{-1}$ characteristic of the O=C–O$^-$ and OH groups, from which it is clear that no free acid is present, since dichloroacetic acid itself shows strong bands in these regions. The strong absorption at 1760 cm.$^{-1}$ in all the polymers shows the presence of combined ester groups, and this is supported by the C–O absorptions at 1268, 1230, and 1200 (no. 5) and 1290, 1255, and 1215 cm.$^{-1}$ (no. 1). Moreover, the intensity of the absorption at 1760 cm.$^{-1}$ is proportional to the chlorine content of the polymer, no. 2 (of high molecular weight and low chlorine content) showing a much weaker absorption here than no. 5. The spectroscopic evidence supports the conclusion, already drawn from chemical analyses and molecular-weight measurements, that the catalyst becomes combined in the polymer as a di- or tri-chloroacetate group, there being one such group per polymer molecule. The band at 680 cm.$^{-1}$ (all samples except no. 5), however, cannot be assigned to C–Cl bending vibrations since it is present in polystyrene prepared by a free-radical mechanism and in polystyrene hydrolysed to remove chloroacetate groups (no. 9); it could be due to C=CH deformation vibrations of residual benzene. The strong band near 760 cm.$^{-1}$ present in all polystyrene samples prevents observation of the C–Cl band in this region.

The band at 816 cm.$^{-1}$ (no. 5) can be correlated with a similar band in the spectrum of benzyl dichloroacetate and may be due to C–O stretching vibrations which are sensitive to the mass of the polymer chain. The bands at 828 (no. 2) and 830 cm.$^{-1}$ (nos. 1 and 13) can be similarly assigned. Comparison of the spectrum of the hydrolysed polymer (no. 9) with that of no. 1 shows that the strong absorption at 1760 cm.$^{-1}$ has almost disappeared and the bands at 1290 and 1255 cm.$^{-1}$ are missing. The band at 830 also has been lost, permitting the observation of the 844 cm.$^{-1}$ band due to C=CH deformation vibrations in the benzene ring, which can be seen also in polystyrene prepared by a radical mechanism and no. 4. The bands at 1180 and 967 cm.$^{-1}$ are also much reduced in intensity in the hydrolysed polymer which suggests that they also are associated with the chloroacetate group. Clearly this group has been removed by hydrolysis. New weak bands at 3350, 1303, and 1110 in the hydrolysed polymer may arise from the replacement of the chloroacetate group by a hydroxyl group. It is not possible to determine whether hydrolysis leads to the formation of terminal unsaturation since the bands at 980 and 967 cm.$^{-1}$ (no. 9) due to unsaturation are also present in the unhydrolysed polymers (965 and 983 cm.$^{-1}$ in no. 1). This unsaturation in the polymer may arise through loss of a small proportion of terminal chloroacetate groups, or by the existence of a minor termination mechanism not involving catalyst recombination, or it may appear along the polymer chain in some way. Since chemical analysis revealed no unsaturation, it is clear that it is very limited.

The Rôle of Water.—Since water was shown to be a cocatalyst for polymerisation in absence of solvent (Part VII) it is possible that the proton which is donated to the monomer by the catalyst–cocatalyst complex is derived from water. A polymer, prepared in the absence of water but in the presence of deuterium oxide (no. 11), showed no band in the region of 2180 cm.$^{-1}$, which can be assigned to the C–D stretching frequency. This suggests that the proton is donated exclusively by the acid, and the function of water in initiation is obscure. Evidently no exchange of hydrogen between water and the acid occurs at the initiating step of the reaction.

The Influence of Solvents.—Increased dielectric constant of the medium greatly enhances the rate of polymerisation, and no dependence of rate on water could be discovered for ethylene dichloride solutions (Part VII). Mechanisms involving ions derived from the solvent have been invoked to account for the absence of obvious cocatalysis in the polymerisation of styrene catalysed by titanium tetrachloride.[5] Infrared spectroscopy might

[5] Plesch, "Cationic Polymerisation," Heffer, Cambridge, 1953.

reveal the occurrence in the polymer of groups derived from the solvent. The positions of the absorption bands in nos. 13 and 18 are virtually identical, and so no bands are present in no. 18 which could be associated with terminal $CH_3{\cdot}[CH_2]_4{\cdot}$ groups. Such groups would absorb [6] at 720—740, 760—780, 1070, and 1480 cm.$^{-1}$, and strong bands already occur in these regions which would mask any bands due to *n*-butyl groups and so their detection is not possible.

Comparison of nos. 13 and 17 shows that no. 17 has a new band at 843 and the bands at 965 and 978 cm.$^{-1}$ are absent. No nitrogen was found in the polymer prepared in nitromethane (no. 17) and it shows no bands which could be correlated with the nitromethyl group (1510—1560 and 1300—1350 cm.$^{-1}$) which would arise if $O_2N{\cdot}CH_2^-$ ions became incorporated. Again it can be concluded that ions from the solvent are not incorporated in the polymer, and the observed differences in the spectra of nos. 13 and 17 can be attributed to the different molecular weights of the polymers, since comparison of nos. 1 and 4, and nos. 2, 5, and 13 shows clearly that molecular-weight differences cause many minor differences in the spectra.

Sample no. 16, prepared in ethylene dichloride, shows new bands at 800 and 1290 cm.$^{-1}$ when compared with no. 13, whilst the band at 860 is missing and bands at 945, 965, 978, and 998 are replaced by one at 985, and bands at 1110, 1135, and 1195 by one at 1160 cm.$^{-1}$. Incorporation of chloroethyl residues would lead to bands at 680, 720—740, 1070, and 1480 cm.$^{-1}$ but since absorptions are already present at 680, 700, 1064, and 1470 cm.$^{-1}$ they would tend to be obscured. There is therefore no evidence for the incorporation of solvent ions, and the discrepancies may again be due to molecular-weight differences.

Experimental

For general details see Parts VI and VII (preceding papers). Viscosities were measured at 25° with Ostwald dilution viscometers with flow times greater than 100 sec. for benzene. The infrared spectra were measured with Hilger single-beam D209 and Grubb-Parsons double-beam instruments. The polymers were hydrolysed by refluxing them for several hr. with potassium hydroxide in octyl alcohol.

We are indebted to C. R. Davies, of the Shell Petroleum Co., and M. St. C. Flett, of Imperial Chemical Industries Limited, in whose laboratories the infrared spectra were measured; to P. H. Plesch for valuable discussions on the interpretation of the spectra; and to Mrs. S. M. Bark for the microchemical analyses.

The University, Nottingham.
[Present Address (A. R. M.).—University College, Ibadan, Nigeria.]

[*Received, December 10th*, 1956.]

[6] Plesch, *J.*, 1953, 1653.

718. *The Kinetics of Catalytic Polymerisations. Part IX.* The State of the Chloroacetic Acids in Solution.*

By C. P. Brown and A. R. Mathieson.

The dimerisation and hydration of the chloroacetic acids in organic solvents is discussed. In inert solvents of low dielectric constant the acids exist very largely as dimers but high dielectric constant and ability of the solvent to form hydrogen bonds lead to considerable dissociation of the dimers. In a given solvent the more highly chlorinated acids are more highly associated. The association of acetic acid and the three chloroacetic acids has been studied in styrene and α-methylstyrene by a partition method, and cryoscopically in styrene in the presence and absence of water. The hydration of these acids in styrene and α-methylstyrene has been estimated. The presence of water causes dissociation of the dimers and reduces the strength of their hydrogen bonds. The cryoscopic constant of styrene is 4·32, and its freezing point −30·4°.

To formulate a mechanism for the chloroacetic acid-catalysed polymerisation of styrene we must identify the chemical species responsible for initiation, and so must know the nature of the acid species present and their concentrations.

The association of the chloroacetic acids in solution has already been studied in many solvents, and we have interpreted the data [1] relating to the partition of acetic acid and the chloroacetic acids between water and various organic solvents. The equilibria involved in these partitions can be represented as

$$H^+ + R{\cdot}CO_2^- \text{ (aq.)} \rightleftharpoons R{\cdot}CO_2H \text{ (aq.)}$$

$$R{\cdot}CO_2H \text{ (aq.)} \rightleftharpoons R{\cdot}CO_2H \text{ (org.)}$$

$$(R{\cdot}CO_2H)_2 \text{ (org.)} \rightleftharpoons 2R{\cdot}CO_2H \text{ (org.)}$$

and the first two equilibria may be written stoicheiometrically as

$$\text{Total acid (aq.)} \rightleftharpoons R{\cdot}CO_2H \text{ (org.)}$$

Two equilibrium constants define the system

$$K_1 = [R{\cdot}CO_2H \text{ (org.)}]/[\text{total acid (aq.)}] \text{ and } K_2 = [R{\cdot}CO_2H \text{ (org.)}]^2/[(R{\cdot}CO_2H)_2 \text{ (org.)}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

If c and f are the concentration and activity coefficient (moles l.$^{-1}$) in the aqueous phase, and c' the concentration in the organic phase,

then $$c'/cf = K_1 + 2K_1^2cf/K_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

By plotting cf against c'/cf, values of both K_1 and K_2 were obtained for the four acids in a number of solvents. All these results refer to water-saturated systems and both monomeric and dimeric species may be hydrated. The value of K_1 increases with the dielectric constant of the organic solvent. The value of K_2 is very low (*i.e.*, the acid exists very largely as dimer) in inert media of low dielectric constant, but high dielectric constant and ability of the solvent to form hydrogen bonds encourage the dissociation of the dimers. In a given solvent the more highly chlorinated acids are more highly associated.

Bell, Baughan, and Vaughan-Jackson [2] studied the association of the three chloroacetic acids in *p*-chlorotoluene cryoscopically and found that between 0·05 and 0·35 mole l.$^{-1}$ they are almost wholly present as dimers. The influence of water on the association of

* Part VIII, preceding paper.

[1] Brown and Mathieson, *J. Phys. Chem.*, 1954, **58**, 1057.

[2] Bell, Baughan, and Vaughan-Jackson, *J.*, 1934, 1968.

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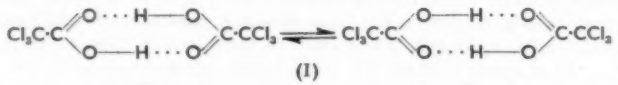
trichloroacetic acid in benzene has been examined cryoscopically by Bell and Arnold,[3] who concluded that in dilute solutions most of the acid exists as the hydrated monomer $CCl_3{\cdot}CO_2H,H_2O$, but above 0·7 moles $l.^{-1}$ there is also present a significant amount of the dimeric dihydrate $(CCl_3{\cdot}CO_2H,H_2O)_2$. Clearly the dimeric dihydrate is less stable than the unhydrated dimer. Bell [4] (see also ref. 7) has suggested possible structures for these species. The unhydrated dimer may be represented as (I) and the hydrated monomer as (II) or (III)

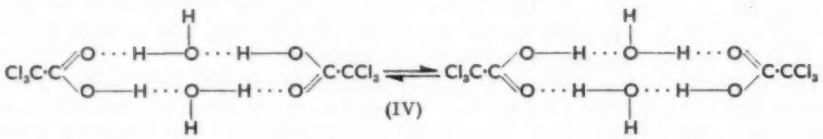


(I)

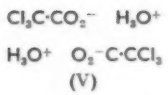
(II)

$Cl_3C{\cdot}CO_2^-,H_3O^+$ or $Cl_3C{\cdot}CO_2H_2{\cdot}OH^-$ (III)

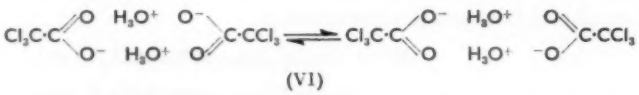
Similarly the dimeric dihydrate may be (IV), (V), or (VI) : [5]



(IV)



(V)



(VI)

It is not certain whether the hydrogen-bonded or the ionic form corresponds more closely with the actual structure. Davies, Jones, Patnaik, and Moelwyn-Hughes [6] believe that the bonding in the dimers is largely electrostatic, and this is supported by our conclusions [1] that high dielectric constant favours dissociation and that the more highly chlorinated acids are more highly associated, but the dissociation of the dimers in hydrogen-bonding solvents of low dielectric constant suggests that the hydrogen-bonded structures may contribute something to the state of the molecule.

The dimerisation and the hydration of the chloroacetic acids were studied in styrene and in α-methylstyrene by partition and cryoscopic methods and the hydration of the acids estimated.

Results and Discussion

Partition of the Chloroacetic Acids between Styrene and α-Methylstyrene, and Water.—The partition results for the three chloroacetic acids and acetic acid distributed between styrene and water, and α-methylstyrene and water, at 25°, are summarised in Table 1. Fig. 1 shows a plot of c'/cf against cf for the four acids distributed between styrene and water, and illustrates the agreement of the results with eqn. (2), from which the values of K_1 and K_2 are calculated. The values of f were obtained from results quoted in ref. 1.

The values of both K_1 and K_2 increase from acetic to dichloroacetic acid but are lower for trichloroacetic acid. Evidently dichloroacetic acid is appreciably less dimerised than trichloroacetic acid, particularly in styrene.

[3] Bell and Arnold, *J.*, 1935, 1432.
[4] Cf. Sidgwick, *Ann. Reports*, 1934, **31**, 40.
[5] Brown and Mathieson, *Ricerca Sci.*, 1955, **25**, Suppl. Simp. Int. Chim. Macromol.
[6] Davies, Jones, Patnaik, and Moelwyn-Hughes, *J.*, 1951, 1249.

TABLE 1. *Partition of the acids between water, and styrene and α-methylstyrene.*

	Styrene				α-Methylstyrene			
Acid	10^3K_1	10^3K_2	n	Dimer (moles %)	10^3K_1	10^3K_2	n	Dimer (moles %)
Acetic	2·0	0·44	1·7	82	3·6	2·0	1·6	75
Monochloroacetic	11	11	1·5	67	9·1	13	1·4	57
Dichloroacetic	59	89	1·4	57	22	14	1·4	57
Trichloroacetic	14	1·8	1·8	89	6·5	0·62	1·9	95

The partition can also be written stoicheiometrically as

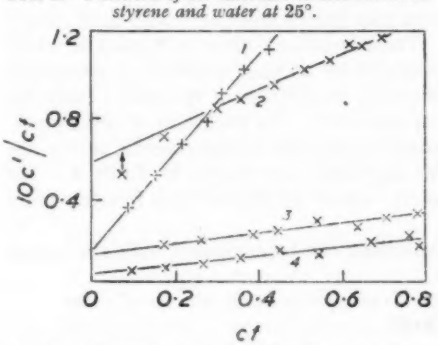
$$n\ R{\cdot}CO_2H\ (aq.) \rightleftharpoons (R{\cdot}CO_2H)_n\ (org.)$$

where n is the stoicheiometric degree of association in the organic phase. Hence $c'/(cf)^n = K$

and
$$\log c' = \log K + n \log cf \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

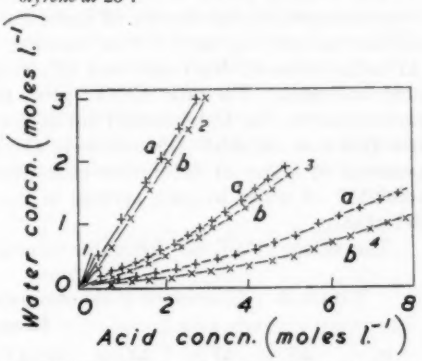
from which values of n can be obtained. Plots of log c' against log cf are linear over large ranges of concentration, indicating that n is insensitive to concentration when this is not

FIG. 1. *Partition of the chloroacetic acids between styrene and water at 25°.*



1, Trichloroacetic; 2, dichloroacetic; 3, monochloroacetic; 4, acetic acid.

FIG. 2. *Effect of the chloroacetic acids on the solubility of water in styrene and in α-methylstyrene at 25°.*



1, Trichloroacetic; 2, dichloroacetic; 3, monochloroacetic; 4, acetic acid; *a*, α-methylstyrene; *b*, styrene.

too low. Table 1 includes the values of n so obtained and the corresponding percentage of the acid in the organic phase present in the dimeric form.

Hydration of the Acids in the Organic Phase.—Since in the partition experiments the organic phase is always water-saturated, and some water is necessary for polymerisation, the solubility of water in styrene and α-methylstyrene solutions of the acids was determined.

TABLE 2. *Hydration of the acids (mole ratios [water]/[acid]) at 25°.*

Solvent	$CH_3{\cdot}CO_2H$	$CH_2Cl{\cdot}CO_2H$	$CHCl_2{\cdot}CO_2H$	$CCl_3{\cdot}CO_2H$
Benzene	0·15	0·20	0·60	1·07
Styrene	0·25	0·51	1·25	1·30
α-Methylstyrene	0·20	0·54	1·30	1·11

The results are shown in Fig. 2. The variation of the water solubility with acid concentration approaches linearity at high acid concentrations, and Table 2 shows the mole ratios [water]/[acid] for this "linear" region, together with Bell's results [7] for benzene

[7] Bell, *Z. phys. Chem.*, 1930, *A*, **150**, 20.

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solution. The degree of hydration increases with the acid strength, exceeding unity for di- and tri-chloroacetic acid. It seems likely that this implies almost complete hydration of the acid species—monomeric and dimeric—in water-saturated solutions. However, no crystalline hydrate could be identified by measurements of the vapour pressure of a saturated solution of water in a styrene–trichloroacetic acid mixture from which the styrene was being progressively removed by evaporation in an apparatus similar to that described by Mathieson.[8]

Freezing-point Depression.—The association of the chloroacetic acids in styrene was studied cryoscopically in the presence of different concentrations of water. It was first necessary to determine the freezing point and cryoscopic constant of styrene. The calorimeter employed for the freezing-point measurements was that described by Brown, Mathieson, and Thynne,[9] and the equilibrium method was used. The freezing point of pure styrene was $-30{\cdot}4° \pm 0{\cdot}1°$, which differs somewhat from that previously reported ($-33°$).[10]

Carbon tetrachloride was chosen as solute for the determination of the cryoscopic constant of styrene, since it seemed most likely to exhibit ideal behaviour. Even so, as some deviation from ideality is expected, plots of $\Delta T/m$ against m must be extrapolated to zero concentration (ΔT = freezing-point depression, m = molality of solute). The three sets of results differ slightly but all extrapolate linearly to the same value of $\Delta T/m$ at zero concentration, **4·32**, and this is the cryoscopic constant of styrene.

The freezing points of solutions of acetic and the three chloroacetic acids in styrene were measured in the absence of water by Brown and Bury's method,[11] who used sodium sulphate as a drying agent within the solution. These results are given in Table 3, in which ΔT is the observed depression and ΔT_i that calculated for an ideal solution of monomeric acid molecules. The ratio $\Delta T_i/\Delta T$ gives the degree of association of the acid. Since the measurements had to be carried out at low temperatures careful exclusion of atmospheric moisture was essential. Results were also obtained for di- and tri-chloroacetic acid in the presence of water at saturation concentration, and these are shown in Table 4. The solubility of water in pure styrene is too low at $-30{\cdot}4°$ to depress the freezing point detectably.

The values of $\Delta T_i/\Delta T$ for water-saturated solutions can be compared with the values

TABLE 3. *Association of the chloroacetic acids in styrene in the absence of water below* $-30{\cdot}4°$.

m	ΔT	$\Delta T/m$	$\Delta T_i/m$	$\Delta T_i/\Delta T$	m	ΔT	$\Delta T/m$	$\Delta T_i/m$	$\Delta T_i/\Delta T$
Acetic acid					Dichloroacetic acid				
0·25	0·62	2·48	4·24	1·71	0·22	0·46	2·09	4·24	2·03
0·40	1·01	2·51	4·18	1·67	0·37	0·77	2·09	4·26	2·01
0·64	1·53	2·39	4·13	1·73	0·60	1·24	2·07	4·14	2·00
0·93	2·26	2·43	4·04	1·66	0·81	1·67	2·06	4·08	1·98
1·26	3·03	2·40	3·94	1·64	1·07	2·11	1·97	4·00	2·03
Monochloroacetic acid					Trichloroacetic acid				
0·21	0·49	2·32	4·24	1·83	0·097	0·20	2·11	4·29	2·03
0·39	0·85	2·19	4·19	1·91	0·15	0·32	2·13	4·28	2·01
0·68	1·49	2·19	4·13	1·89	0·27	0·58	2·15	4·23	1·97
0·97	2·12	2·18	4·03	1·85	0·38	0·81	2·12	4·20	1·98
1·38	3·04	2·20	3·98	1·81	0·49	1·04	2·12	4·17	1·97

of n from the partition experiments, though it must be remembered that they refer to $-30{\cdot}4°$ and $+25°$, respectively. The values of $\Delta T_i/\Delta T$ are somewhat lower, and appear to decrease with increasing concentration; nevertheless both methods indicate a bigger

[8] Mathieson, *J.*, 1949, S 294.
[9] Brown, Mathieson, and Thynne, *J.*, 1955, 4141.
[10] Cf. Heilbron and Bunbury, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1943, Vol. 3, p. 643.
[11] Brown and Bury, *J. Phys. Chem.*, 1926, **38**, 694.

degree of association for trichloroacetic acid than for dichloroacetic acid, and when the different experimental conditions are considered, the values are in reasonable accord.

The values of $\Delta T_i/\Delta T$ in Tables 3 and 4 show clearly that the tendency to dimerise increases with the chlorine content of the acid, the dimerisation initially being complete

TABLE 4. *Association of di- and tri-chloroacetic acid in styrene saturated with water below* 30·4°.

m	ΔT	$\Delta T/m$	$\Delta T_i/m$	$\Delta T_i/\Delta T$	m	ΔT	$\Delta T/m$	$\Delta T_i/m$	$\Delta T_i/\Delta T$
	Dichloroacetic acid					Trichloroacetic acid			
0·41	1·07	2·60	4·18	1·61	0·13	0·31	2·41	4·29	1·78
0·77	2·37	3·08	4·09	1·33	0·24	0·62	2·57	4·24	1·65
0·86	2·68	3·12	4·06	1·30	0·30	0·84	2·79	4·22	1·51
0·97	2·91	3·00	3·93	1·31	0·38	1·06	2·80	4·20	1·50

for di- and tri-chloroacetic acid. The addition of water decreases the degree of dimerisation quite markedly.

Effect of Water on the Extent of Dimerisation.—Di- and tri-chloroacetic acid are almost completely dimerised in water-free styrene solution. In solvents of higher dielectric constant and particularly those which can form hydrogen bonds, the degree of dimerisation is markedly reduced.[1] Water also facilitates the dissociation of the dimeric forms of the acids. Even in styrene, in the presence of water the concentration of the hydrated monomeric species (II or III) is considerable. In water-saturated solutions both monomer and dimer are fully hydrated, and presumably exist as (II) or (III) and (IV), (V), or (VI) respectively. Clearly the bonding is weaker in the dimeric dihydrate than in the unhydrated dimer, and this may be important in explaining both the rôle of water in the polymerisations and their high kinetic order with respect to the acid catalyst.

It is possible to obtain a more quantitative estimate of the effect of water on the dissociation of the dimers. In water-saturated and water-free solutions respectively, the association can be written as

$$2R{\cdot}CO_2H,H_2O \rightleftharpoons (R{\cdot}CO_2H,H_2O)_2 \quad K_2 = [R{\cdot}CO_2H,H_2O]^2/[(R{\cdot}CO_2H,H_2O)_2]$$

and

$$2R{\cdot}CO_2H \rightleftharpoons (R{\cdot}CO_2H)_2 \quad K_3 = [R{\cdot}CO_2H]^2/[(R{\cdot}CO_2H)_2]$$

If C_1 and C_2 are the concentrations of acid present as monomer and dimer respectively, then the degree of association

$$n = \Delta T_i/\Delta T = (C_1 + 2C_2)/(C_1 + C_2)$$

Also K_2 (or K_3) $= C_1^2/2C_2$.

Hence K_2 (or K_3) $= C_1(1 - n/2)/(n - 1)$ and values of K_2 and K_3 can be obtained at −30·4° from the freezing-point data for di- and tri-chloroacetic acid. Values of ΔG_2° and ΔG_3°, the corresponding standard free-energy changes, can be calculated; they are 630 and 4460 cal. respectively for dichloroacetic acid and 1460 and 4590 cal. for trichloroacetic acid at −30·4°. The values for ΔG_3° (−30·4°) are only accurate to ±50%, since the values of n are close to 2·00; even so ΔG_3° clearly exceeds ΔG_2° by about 3 kcal. Thus water reduces the free energy of dissociation of the dimer by about 75%.

EXPERIMENTAL

Partition.—Aqueous solutions (20 ml.) of the chloroacetic acids of various concentrations were added to styrene (20 ml.) or α-methylstyrene (20 ml.) in 50-ml. vessels, and equilibrated for 2—3 hr. at 25° ± 0·01° with continuous agitation. The layers were separated and titrated with 0·1 or 0·01N-alkali solutions.

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Water Solubilities.—Water was added from a microburette to solutions of the chloroacetic acids in styrene or α-methylstyrene until turbidity appeared.

Freezing Point and Cryoscopic Constant of Styrene.—The calorimeter described by Brown, Mathieson, and Thynne [9] was used, except that the mixing vessel was replaced by a glass vessel which fitted closely into the innermost Dewar vessel, and carried a stirrer, platinum resistance thermometer, dropping pipette, and sampling tube. Styrene, purified and dried, was distilled into this glass vessel which was then closed and placed in a solid carbon dioxide–alcohol freezing bath. A film of solid styrene formed on the inner surface of the vessel and was shaken free from time to time. In this way, 250 ml. of a sludge of liquid and solid styrene were prepared, containing about 50% of solid. The glass vessel was introduced into the inner Dewar vessel which was surrounded by the cryostatic liquid (solid carbon dioxide–alcohol), kept about 1° below the temperature of the inner Dewar vessel by addition of solid carbon dioxide and the use of a 20-junction thermocouple. The inner Dewar vessel carried a metal lid which also dipped into this cryostatic liquid. The calorimeter was assembled, stirring commenced at 60 revs. per min., and the apparatus left for 2 hr. to attain equilibrium. The temperature of the styrene sludge was measured by the platinum resistance thermometer.

Concentrated solutions of carbon tetrachloride in styrene, previously cooled to the equilibrium temperature, were placed in the dropping pipette and added to the styrene sludge without opening the calorimeter by raising a projecting glass rod which controlled the dropping pipette. 20 min. were allowed for equilibrium to be attained after the addition of carbon tetrachloride solution, the temperature was read and stirring discontinued. The sampling tube, previously evacuated to 10—20 mm. pressure, was opened to the solution and a suitable quantity withdrawn for analysis.

The carbon tetrachloride solutions in styrene were analysed densitometrically. The pycnometer was a 5-ml. glass bulb carrying a capillary tube, and this was calibrated at 25° with water and a cathetometer.

Freezing points of solutions of chloroacetic acid in styrene were determined in the same way as the carbon tetrachloride solutions, but the solutions were analysed by alkali titration. For the experiments in the absence of water the glass vessel contained 10 g. of anhydrous sodium sulphate (" AnalaR "). Otherwise, the required amount of water was added with the chloroacetic acid.

No polymerisation occurred in any of these experiments.

Materials.—Carbon tetrachloride was washed with alcoholic potassium hydroxide and with water, dried ($CaCl_2$), and fractionated. The chloroacetic acids, styrene, and α-methylstyrene were purified as described previously.[11]

THE UNIVERSITY, NOTTINGHAM.
[Present Address (A. R. M.).—UNIVERSITY COLLEGE, IBADAN, NIGERIA.]

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[11] Brown and Mathieson, Part VI, *J.*, 1957, 3608.

719. *The Kinetics of Catalytic Polymerisations. Part X.* The Mechanism of the Polymerisation of Styrene catalysed by Chloroacetic Acids.*

By C. P. Brown and A. R. Mathieson.

A mechanism is suggested for the polymerisation of styrene catalysed by di- and tri-chloroacetic acid which is in agreement with the dependence of reaction rate and polymer molecular weight and constitution on reactant concentrations, dielectric constant, and temperature. Initiation involves the endothermic formation of a monomer–catalyst polarisation complex which is slowly and spontaneously converted into an ion-pair. The propagation step involves the catalyst, either as solvating the growing polymeric cation, or as addition of the monomer–catalyst complex to the growing cation. The necessity for this is diminished by increasing polarity of the medium. Termination involves spontaneous recombination of ions, and transfer to monomer also takes place. The formation of the monomer–catalyst complex explains the very rapid initial consumption of catalyst and the increase of activation energy with dielectric constant. The function of water as a cocatalyst for the polymerisation in absence of solvent is due to its dissociating effect on the dimeric forms of the acids, leading to more active monomeric forms. In media of higher dielectric constant this is unnecessary.

The polymerisation of styrene catalysed by di- and tri-chloroacetic acid without solvent and in ethylene dichloride and nitromethane has been described in the preceding papers. Originally studied because it was felt that a hydrogen acid might prove to be a catalyst which functioned by a simpler mechanism, these reactions possess many complicated features which are not exhibited by the metal halide-catalysed polymerisations. Consequently the problem of devising a polymerisation mechanism is considerable.

The principal features requiring explanation are as follows :

The Rate of Monomer Consumption.—From kinetics determined from the initial rates of polymerisation,

$$-\mathrm{d[M]}/\mathrm{d}t = k\,[\mathrm{M}]^2[\mathrm{C}]^{3\cdot5}[\mathrm{W}] \text{ without solvent} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$-\mathrm{d[M]}/\mathrm{d}t = k'[\mathrm{M}]^2[\mathrm{C}]^2 \text{ in ethylene dichloride} \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$-\mathrm{d[M]}/\mathrm{d}t = \mathrm{k''}[\mathrm{M}]^2[\mathrm{C}] \text{ in nitromethane} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where [M] = monomer concentration, [C] = acid concentration, and [W] = water concentration. The rate is always proportional to the square of the monomer concentration but the kinetic order with respect to the acid increases from unity to 3·5 as the dielectric constant of the medium is reduced from 31 to 2. Also, in the absence of solvent, water is an essential cocatalyst. The kinetics are the same for both acids but the overall rate constants are always much larger for trichloroacetic acid.

The Rate of Acid Consumption.—The initial rate of acid consumption is far too great to be accounted for by the acid incorporated in the polymer, and it is likely that some kind of complex is formed initially between the acid and the monomer. The Figure shows a plot of the mole ratio y = (monomer consumed)/(acid consumed) against the extent of reaction (p) = (moles of monomer polymerised)/(moles of monomer originally present). A linear relation exists between these quantities which obeys the equations

$$y = 0{\cdot}5 + 15{\cdot}6p \text{ (dichloroacetic acid catalysis without solvent)} \quad . \quad . \quad (4)$$

$$y = 1{\cdot}7 + 15{\cdot}6p \text{ (dichloroacetic acid catalysis in ethylene dichloride)} \quad . \quad (5)$$

$$y = 0{\cdot}5 + 1{\cdot}6p \text{ (trichloroacetic acid catalysis without solvent)} \quad . \quad . \quad (6)$$

$$y = 2{\cdot}3 + 0{\cdot}9p \text{ (trichloroacetic acid catalysis in ethylene dichloride)} \quad . \quad (7)$$

* Parts VI—IX, preceding papers.

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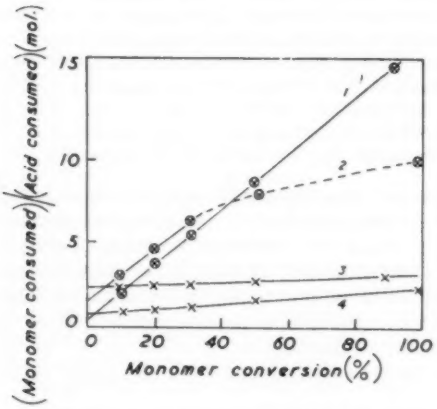
The values of y when $p = 0$ suggest the existence of a complex MC_2 in the absence of solvent and a complex M_2C in ethylene dichloride solution, or perhaps a series of complexes M_nC_y with MC_2 and M_2C as their stoicheiometrical equivalents. The formation of polarisation complexes between these substances would not be surprising on chemical grounds.

Influence of Monomer and Catalyst Concentrations on the Molecular Weight (M) of the Polymer.—The two catalysts produce polymers of almost the same molecular weight under the same conditions, and the following relations are obeyed :

$$M = 1100 + 200[M] = 1100 + 120[C] \text{ (ethylene dichloride solution)} \quad . \quad (8)$$

$$M = 975 + 70[M] = 1000 + 190[C] \text{ (nitromethane solution)} \quad . \quad . \quad . \quad (9)$$

The form of these expressions suggests that a chain-transfer mechanism is operating.



Ratios of monomer and acid consumed: **1**, *dichloroacetic acid without solvent*; **2**, *dichloroacetic acid in ethylene dichloride*; **3**, *trichloroacetic acid in ethylene dichloride*; **4**, *trichloroacetic acid without solvent.*

Effect of Dielectric Constant.—This is described by

$$-d[M]/dt = Ke^{\alpha D} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$\log M = B + C(D - 1)/(2D + 1) \quad . \quad . \quad . \quad . \quad . \quad (11)$$

The molecular weight increases only slightly with increased dielectric constant, but the reaction rate is greatly increased, which is a recognised feature of cationic polymerisations.

The Constitution of the Polymer.—The polymer incorporates one catalyst fragment per polymer molecule under all conditions. The very small amount of residual unsaturation indicated by infrared analysis is unlikely to be kinetically significant. No solvent fragments are incorporated, and neither is the water cocatalyst.

The Overall Energies of Activation (E_o).—These increase with the dielectric constant and hence with the rate of polymerisation. This feature has been observed before in cationic polymerisations.

Conductance.—An increase of conductance is associated with a decrease in reaction rate.

Dimerisation and Hydration.—The acid catalysts are dimersed and hydrated.

Retardation.—The polymerisation is retarded and the molecular weight reduced by quinones. A complete explanation for this has already been given (Part VII).

Any explanation of these phenomena must be based on the known chemical species present. It has been shown (Part IX) that the acid exists in four forms, *i.e.*, monomer and dimer and their hydrates, which can be represented as C, C_2, CW, and C_2W_2. The last three can be considered to be hydrogen-bonded complexes, or alternatively ion-pairs.

Complex-formation occurs between styrene and the acids, and complexes MC_2 (without solvent) and M_2C (in ethylene dichloride) have been postulated. An intermediate complex MC seems likely to occur in each case also and is required to explain the kinetics.

The Polymerisation Mechanism

It is proposed to interpret the kinetics in terms of a stationary-chain mechanism, since this type of mechanism has proved very successful in explaining cationic polymerisation. The reactions showed no sign of non-stationary conditions and the chain lengths were sufficiently great to make the stationary-chain mechanism feasible. Nevertheless the possibility must be borne in mind that the reactions proceed by a stepwise addition process.

The Polymerisation in Ethylene Dichloride Solution.—The sequence of reactions which represents the results for this system can be written as follows:

1.	$M + C \rightleftharpoons MC$	K_1
2.	$MC + M \rightleftharpoons M_2C$	K_2
3.	$MC \longrightarrow M^+C^-$	k_i
4.	$M_n^+C^- + MC \longrightarrow M_n^+C^- + C$	k_p
5.	$M_n^+C^- + MC \longrightarrow M_nC + M^+C^-$	k_{tr}
6.	$M_n^+C^- \longrightarrow M_nC$	k_t

The first two equilibria lead to the formation of monomer–catalyst complexes and are responsible for the initial rapid consumption of catalyst. Step 2 plays no part in the polymerisation. Initiation (step 3) in envisaged as a conversion of the complex MC into an ionised complex M^+C^-, and propagation (step 4) results in the growth of the M^+ ion with the C^- ion in attendance to form an ion-pair. This growth suffers spontaneous termination (step 6) with recombination of the ions. An alternative to propagation is monomer transfer (step 5). Propagation and transfer are written as requiring reaction with the monomer–catalyst complex MC rather than with free monomer. An alternative formulation could be made in terms of solvation by the catalyst of the polymerising ion, and reaction with pure monomer, *i.e.*,

$$4a.\ (M^+C^-)C + M \longrightarrow (M_2^+C^-)C$$

$$5a.\ (M_n^+C^-)C + M \longrightarrow M_nC + (M^+C^-)C$$

Initiation is given as the rearrangement of the complex MC to give an ion-pair, but the ion-pair could arise directly from a monomer–catalyst collision:

$$3a.\ M + C \longrightarrow M^+C^-$$

Reactions 3*a*, 4*a*, and 5*a* are kinetically indistinguishable from reactions 3, 4, and 5 and probably represent merely alternative ways of writing essentially the same processes. The monomeric form of the catalyst is shown as the active catalytic species; this is likely on chemical grounds since the dimeric form is more stable, and is further suggested by a comparison of the kinetics in the absence of solvent and in ethylene dichloride and nitromethane solution and the interpretation of the function of water in the reaction without solvent. The true catalytic species may actually be the hydrate CW but there is no direct evidence for this as in the polymerisation without solvent.

Application of the stationary-state hypothesis leads kinetically to

$$V_i = V_t \text{ and so } [M_n^+C^-] = k_iK_1[M][C]/k_t$$

The rate of polymerisation is then

$$V_p = -d[M]/dt = k_p[M_n^+C^-][MC] = k_pk_iK_1[M]^2[C]^2/k_t \quad . \quad . \quad (12)$$

in agreement with observation. The chain length of the polymer (n) is $V_p/(V_t + V_{tr})$ and hence

$$1/n = k_{tr}/k_p + k_t/k_pK_1[M][C] \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

Thus $1/n \propto 1/[M]$ and $1/n \propto 1/[C]$. These relations are obeyed and a value of $k_p/k_{tr} = 21$ is obtained. Incorporation of one catalyst fragment in each polymer molecule is demanded by steps **5** and **6**.

The detailed molecular and electronic processes involved in the various steps of the polymerisation will be considered later.

The Polymerisation in Nitromethane Solution.—No evidence was obtained for monomer–catalyst complex formation in this system because the consumption of the acid catalyst could not be studied, but by analogy with the other systems, and by the interpretation given to the energies of activation it may be assumed to occur. The best reaction scheme is

1.	$M + C \rightleftharpoons MC$	K_1
2.	$MC \longrightarrow M^+C^-$	k_i
3.	$M^+C^- + M \longrightarrow M_2^+C^-$	k_p
4.	$M_n^+C^- + MC \longrightarrow M_nC + M^+C^-$	k_{tr}
5.	$M_n^+C^- \longrightarrow M_nC$	k_t

Propagation (step 3) involves the free momomer; alternatively, catalyst solvation of the polymerising ion may be unnecessary, the dielectric constant of the medium being so much higher. The transfer process (step 4), however, needs the participation of catalyst either as the complex MC or as a solvate if all the polymer molecules are to contain one catalyst fragment. It may be, however, that only a relatively small number of growing polymer chains are terminated by monomer transfer in which case this could occur as

$$4a.\ M_n^+C^- + M \longrightarrow M_n + M^+C^-$$

and the small number of polymer molecules free from catalyst fragments might be overlooked.

There is some doubt in this system whether the polymerising ion-pair $M_n^+C^-$ should be looked upon as a single kinetic unit or whether the ions become independent. An alternative formulation for the step 5 is therefore

$$5a.\ M_n^+ + C^- \longrightarrow M_nC$$

This requires that propagation should involve direct catalyst participation as in ethylene dichloride (cf. 3*a*) :

$$M_n^+ + MC \longrightarrow M^+_{n+1} + C$$

in order to preserve agreement with the observed kinetics.

The stationary-state hypothesis leads to

$$[M_n^+C^-] = k_iK_1[M][C]/k_t$$

and

$$V_p = -d[M]/dt = k_pk_iK_1[M]^2[C]/k_i \quad . \quad . \quad . \quad . \quad . \quad (14)$$

in agreement with experiment.

The chain length of the polymer (n) is given by

$$1/n = k_t/(k_p[M]) + k_{tr}K_1[C]/k_p \quad . \quad . \quad . \quad . \quad . \quad (15)$$

which gives the correct dependence on monomer concentration but not for the catalyst concentration. No explanation has been found for this discrepancy, and no reaction

scheme has been discovered which will explain the increase of n with [C]. Again the true catalytic species may be CW.

The Polymerisation in Absence of Solvent.—The polymerisations are more complex under these conditions, additional features being the extraordinarily high dependence of the rate of polymerisation upon catalyst concentration, and the proved necessity for water. The function of the water seems most likely to be to cause dissociation of the dimeric acid C_2 and formation of the monomeric hydrate CW which is the active catalytic species. This agrees with the observed effect of water on the degree of dimerisation of the acids. The rate of consumption of acid suggests the formation of a complex MC_2, and if this participates in the polymerisation as well as MC, the observed kinetic order can be derived. The reaction scheme is

1.	$M + C \rightleftharpoons MC$	K_1
2.	$M + C_2 \rightleftharpoons MC_2$	K_2
3.	$2C \rightleftharpoons C_2$	K_3
4.	$C + W \rightleftharpoons CW$ (or $C_2 + 2W \rightleftharpoons 2CW$)	K_4
5.	$2CW \rightleftharpoons C_2W_2$	K_5
6.	$M + CW \rightleftharpoons MCW \longrightarrow M^+C^- + W$	k_i
7.	$MC_2 + CW \longrightarrow M^+C^- + C_2 + W$	k_i^1
8.	$M^+C^- + MC \longrightarrow M_2^+C^- + C$	k_p
9.	$M^+C^- + MC_2 \longrightarrow M_2^+C^- + C_2$	k_p^1
10.	$M_n^+C^- + MC \longrightarrow M_nC + M^+C^-$	k_{tr}
11.	$M_n^+C^- \longrightarrow M_nC$	k_t

Possible steps which have been omitted are

(*a*) $MC + CW \longrightarrow M^+C^- + CW$

(*b*) $M + C \longrightarrow M^+C^-$

(*c*) $MC + C \longrightarrow M^+C^- + C$

(*d*) $MC_2 + C \longrightarrow M^+C^- + C_2$

(*e*) $M + C_2W_2 \longrightarrow M^+C^- + CW + W$

(*f*) $MC + C_2W_2 \longrightarrow M^+C^- + C_2W_2$

(*g*) $MC_2 + C_2W_2 \longrightarrow M^+C^- + C_2W_2 + C$

(*a*) and (*f*) are omitted because the function of the catalyst is not clear; (*b*), (*c*), and (*d*) because water is a necessary cocatalyst; (*e*), (*f*), and (*g*) because they lead to a dependence of the rate on $[W]^2$ which is not observed.

Steps 1 and 2 represent monomer–catalyst complex formation, and steps 3, 4, and 5 the dimerisation and hydration of the acids already established. Steps 6 and 7 are both initiation reactions and steps 8 and 9 are alternative propagations. Steps 10 and 11 are transfer and termination as already given for the solution reactions. Steps 8, 9, and 10 can be given the alternative formulation in terms of catalyst solvation of the polymerising ion, and so become

8*a*. $(M^+C^-)C + M \longrightarrow (M_2^+C^-)C$

9*a*. $(M^+C^-)C_2 + M \longrightarrow (M_2^+C^-)C_2$

10*a*. $(M_n^+C^-)C + M \longrightarrow M_nC + M^+C^-$

Application of the stationary-state hypothesis leads to

$$k_t(M_n^+C^-) = k_i[M][CW] + k_i^1[MC_2][CW]$$
$$= K_4[M][C][W]\{k_i + k_i^1K_2K_3[C]^2\}$$
$$\text{Hence } -d[M]/dt = k_p[M_n^+C^-][MC] + k_p^1[M_n^+C^-][MC_2]$$
$$= (K_4/k_t)[M]^2[C]^2[W]\{k_i + k_i^1K_2K_3[C]^2\}\{k_pK_1 + k_p^1K_2K_3[C]\} . \quad (16)$$

which, depending on the relative values of the constants, gives a dependence of rate on catalyst concentration between $[C]^2$ and $[C]^5$. Examination of this equation shows that if K_2 or $K_3 \longrightarrow 0$, $k_i^1 \longrightarrow 0$ and $k_p^1 \longrightarrow 0$ and $-d[M]/dt \propto [C]^2$. Also if $k_i \longrightarrow 0$, $-d[M]/dt \propto [C]^{4-5}$; if $k_i^1 \longrightarrow 0$, $-d[M]/dt \propto [C]^{2-3}$. Since experimentally $-d[M]/dt \propto [C]^{3\cdot5}$, none of these conditions is allowable. However, if $K_1 \longrightarrow 0$, $-d[M]/dt \propto [C]^{2-5}$; if $k_p \longrightarrow 0$, $-d[M]/dt \propto [C]^{3-5}$; if $k_p^1 \longrightarrow 0$, $-d[M]/dt \propto [C]^{2-4}$. Consequently it is possible that steps 1 and 8, or alternatively step 9, may not in fact occur.

The chain length of the polymer (n) is given by

$$\frac{1}{n} = \frac{k_t + k_{tr}[MC]}{k_p[MC] + k_p^1[MC_2]}$$

If $k_p^1 \longrightarrow 0$ this becomes

$$\frac{1}{n} = \frac{k_{tr}}{k_p} + \frac{k_t}{k_pK_1[M][C]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

or if $K_1 \longrightarrow 0$ and $k_p \longrightarrow 0$

$$\frac{1}{n} = \frac{k_t}{k_p^1K_2K_3[M][C]^2} + \frac{k_{tr}K_1}{k_p^1K_2K_3[C]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

Results given in Part VII on the variation of molecular weight (M) during polymerisation without solvent show that

$$M = 680 + 6\cdot80p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

Since p is a function of both [M] and [C], this equation is of the form of equation (a) rather than of (b). This suggests that in fact $k_p^1 \longrightarrow 0$ and that the step 9 originally postulated does not occur. Final kinetic expressions therefore are

$$\frac{-d[M]}{dt} = \frac{k_pK_1K_4}{k_t}[M]^2[C]^2[W](k_i + k_i^1K_2K_3[C]^2) \quad . \quad . \quad . \quad (18)$$

and

$$\frac{1}{n} = \frac{k_{tr}}{k_p} + \frac{k_t}{k_pK_1[M][C]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

Detailed Mechanism of Initiation and Propagation.—The interpretation already given of the variation of the dependence of the rate of polymerisation on acid concentration in different media and of the initial rapid consumption of acid, in terms of monomer–catalyst complex formation, receives support and clarification when other reactions of the chloroacetic acids are considered.

Bell *et al.*[1] studied the acid-catalysed rearrangement of *N*-bromoacetanilide in chlorobenzene solution and found that the Brønsted relation is obeyed

$$\log k_c = a \log K_a + \log G \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

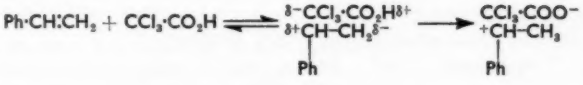
where k_c is the catalytic coefficient, K_a the acid dissociation constant, and a and G are constants. This was taken as indicating that proton transfer occurs, in this particular

[1] Bell and Brown, *J.*, 1936, 1520; Bell, *Trans. Faraday Soc.*, 1938, **34**, 229.

case at least, following the " acidity " of the catalysts as measured in aqueous solution, for acetic and the three chloroacetic acids. For the styrene polymerisation k_0 (overall rate constant) increased in approximately the same proportion as K_a for di- and tri-chloroacetic acid (Part VII) which show the same trend. Whether such a relation is obeyed is however dependent on the nature of the solvent. Thus, for the depolymerisation of paraldehyde catalysed by trichloroacetic acid, Bell [2] gives the relative rates of the reaction in nitrobenzene, benzene, anisole, and ethyl acetate as 1000 : 30 : 1 : 0·01. The low value of the last two relative rates is interpreted in terms of complex formation between the catalyst and the basic oxygen of the solvent. The " apparent " order with respect to the acid concentration varied from 1·6 to 2·5 in different solvents. Caldin and Lidwell [3] observed a similar deviation from simple kinetic behaviour in the acid-catalysed racemisation of optically active ketones in chlorobenzene. In this case extensive complex formation has been confirmed by cryoscopic and polarimetric methods.

The dimerisation of the carboxylic acid catalysts also in many cases appears to play a fundamental rôle in determining the kinetic order of acid-catalysed reactions. In the acid-catalysed rearrangement of *N*-bromoacetanilide [4] the dependence of the rate on catalyst concentration varied with catalyst concentration but was eliminated at low concentrations of catalysts. Even in the absence of demonstrable complex formation considerable effects of the medium are to be expected in solvents of low dielectric constant when carboxylic acids are employed.[5] In aprotic solvents unable to solvate the hydrogen ion the acids will not ionise and acid catalysis must be related to the un-ionised acid molecules. The reaction between ethyl diazoacetate and carboxylic acids, which liberates nitrogen, was studied by Briegleb [6] who concluded that the reaction is kinetically of the second order with respect to the dimeric acid molecules which are supposed to be autocatalytic. Briegleb [6] has also shown that both the monomeric and the dimeric form of the acids possess appreciable moments and can exert a polarising influence. Nernst and Hohmann [7] found the rate of the reaction of 3-methylbut-2-ene with various carboxylic acids, including the chloroacetic acids, to be proportional to the square of the acid concentration both in 3-methylbut-2-ene itself and in benzene solution. They assume the rate to be proportional to $[C_2]$, but an equally good interpretation is that the rate is proportional to $[C_2]^2$. Goldschmidt [3] found the self-esterification of di- and tri-chloroacetic acid in alcohol solution to be of the second order with respect to the acid.

The phenomena of autocatalysis and complex formation are clearly well established in simple reactions of the chloroacetic acids and it is not surprising that they appear in the polymerisations which these acids catalyse. The initiation mechanism suggested for the polymerisations $M + C \rightleftharpoons MC \longrightarrow M^+C^-$ could perhaps be applied equally to the simple reactions. The influence of the medium in promoting the rate would be to facilitate the formation of the active species M^+C^- in media of higher dielectric constant. The variations in kinetic order with different reaction media are to be ascribed to the different degrees of autocatalysis required in media of different dielectric constant. The monomer–catalyst complex could perhaps be represented as a polarisation complex with a finite probability of transition to an ion-pair



The autocatalysis then appears in the propagation step as the reaction of the carbonium

[2] Bell, *J.*, 1936, 1792.
[3] Caldin and Lidwell, *Trans. Faraday Soc.*, 1938, **34**, 236.
[4] Bell and Levinge, *Proc. Roy. Soc.*, 1935, *A*, **151**, 211.
[5] Brønsted and Bell, *J. Amer. Chem. Soc.*, 1931, **53**, 2478.
[6] Briegleb, *Z. phys. Chem.*, 1930, *B*, **10**, 205.
[7] Nernst and Hohmann, *Z. phys. Chem.*, 1893, **11**, 361.

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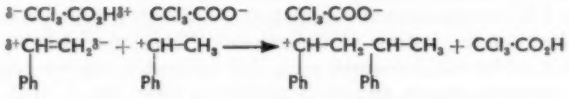
ion with the polarised monomer of a monomer–catalyst complex, the catalyst facilitating this process by its polarising influence on the second monomer :



It seems probable that the dielectric constant of nitromethane is high enough to allow reaction of the carbonium ion with unpolarised monomer molecules and the autocatalytic effect is consequently not observed.

The Increase of Activation Energy with Reaction Rate.—It was observed (Part VII) that, except for the polymerisations in absence of solvent, increased dielectric constant of the medium results in increased overall energy of activation (E_o) as well as increased reaction rate. Solvation of the reactants by catalyst molecules as already envisaged could only lead to a decrease of E_o with increased reaction rate, and so some other effect is masking the normal expected result. The increase in E_o with dielectric constant is associated with an increase in the frequency factor A, which approaches the value predicted by simple collision theory ($\sim 2 \times 10^{11}$) as the dielectric constant is increased. The overall energies of activation can be written as $E_o = E_i + E_p - E_t$ where E_i, E_p, and E_t are the energies of activation of initiation, propagation, and termination respectively. For ethyl bromide solutions, $E_p - E_t = -850$ cal. from the dependence of molecular weight upon temperature. Since molecular weight is little influenced by the dielectric constant of the medium, the value of $E_p - E_t$ is not likely to vary much from one solvent to another. If the approximate value -1 kcal. is assigned to it approximate values of E_i may be obtained. Values of E_o, E_i, and A_i are shown in the Table.

TABLE 1. *Activation Energies and frequency factors.*

Solvent	D	Catalyst	E_o (kcal.)	E_i (kcal.)	A_i
Styrene	2·0	Trichloroacetic acid	9·0	10·0	0·153
Ethyl bromide	4·87	,,	3·0	4·0	—
Ethylene dichloride	10·5	,,	8·0	9·0	1·50
Nitroethane	19·7	,,	10·0	11·0	—
Nitromethane	39	,,	14·0	15·0	$1·9 \times 10^5$
Styrene	2·0	Dichloroacetic acid	5·5	6·5	$5·61 \times 10^{-6}$
Ethyl bromide	4·87	,,	3·0	4·0	—
Ethylene dichloride	10·5	,,	6·0	7·0	$8·09 \times 10^{-5}$
Nitromethane	39	,,	8·0	9·0	1·75

Increase in energy of activation and frequency factor with the dielectric constant of the medium has also been observed in simple reactions. The reactions first kinetically investigated by Menschutkin [9] between amines and halides have been further investigated by Cox and Hawkins [10] and their results show that the value of the frequency factor approaches the collision number in solvents of high polarity, and the activation energy tends towards a maximum value.

One explanation of these phenomena, which evidently occur both in polymer and in " small-molecule " chemistry, is that the activation energies measured are depressed below their " normal " values, the depression being greater in non-polar media. A number of causes may be suggested for this, such as the endothermic formation of a complex before the reaction, the necessity for the ionisation of either of the reactants, or critical orientation conditions for reaction. The influence of the dielectric constant of the medium on

[8] Goldschmidt, *Ber.*, 1896, **29**, 2212.
[9] Menschutkin, *Z. phys Chem.*, 1890, **6**, 41.
[10] Cox and Hawkins, *J.*, 1921, **119**, 142; 1922, **121**, 1170.

the rates of reaction between polar molecules has been given by Laidler and Eyring [11] as

$$\ln k = \ln k_0 - \frac{1}{kT} \cdot \frac{D-1}{2D+1} \cdot \frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_*^2}{r_*^3} + \sum_i \frac{\phi_i}{kT} \quad . \quad . \quad (21)$$

where the μ's and r's are respectively the moments and collision radii of the reactants (A and B) and the activated complex ($_*$), and $\sum_i(\phi_i/kT)$ represents the non-electrostatic contribution. Where a plot of ln k against $(D-1)/(2D+1)$ is non-linear it may be inferred that the non-electrostatic term is important. This is the case for the overall rate of polymerisation (eqn. 10) but is not so for the influence of dielectric constant on molecular weight which gives a linear dependence on $(D-1)/(2D+1)$ (eqn. 11). The latter result is in agreement with a termination mechanism involving recombination of the growing polymeric cation and the catalytic anion such as has been postulated.

The suggestion that the variation of the activation energy with dielectric constant might be explained by the formation of a complex before polymerisation is worth further examination since monomer–catalyst complexes have already been postulated to explain other features of the reactions. Considering the initiation mechanism already postulated

$$M + C \underset{k_1}{\overset{k_1}{\rightleftharpoons}} MC \xrightarrow{k_2} M^+C^-$$

let the energies of activation associated with the velocity constants k_1, k_2, and k_3 be E_1, E_2, and E_3. For the overall initiation, $k_i = k_3k_2/k_1$ and $E_1 = E_2 + E_3 - E_1$. Increase in the dielectric constant of the medium appears to lead to a reduction in the extent of monomer–catalyst complex formation, perhaps through a decrease in the polarising power of the catalyst. This implies that E_2 will be increased, and E_1 decreased, by increase of D, resulting in an overall increase in the activation energy. This gives a reasonable explanation of the results in the Table. There is evidence that the energies of activation of other cationic polymerisations increase with increased dielectric constant of the media (Part VII) and so it may be that some form of endothermic monomer–complex formation occurs in these reactions also. It might be instructive to re-examine the mechanism of other cationic polymerisations in the light of these suggestions.

The initiation mechanism suggested here is essentially that of Taft, Purlee, Ritz, and Defazio.[12] Evans, Jones, Jones, and Thomas,[13] in a study of the trichloroacetic acid-catalysed dimerisation of 1 : 1-di-*p*-tolylethylene, prefer the formulations

$$\text{olefin} + \text{acid} \rightleftharpoons \text{carbonium ion} \rightleftharpoons \text{coloured complex}$$

$$\text{or olefin} + \text{acid} \rightleftharpoons \text{carbonium ion}$$

$$\Downarrow$$

$$\text{coloured complex}$$

THE UNIVERSITY, NOTTINGHAM.
[Present Address (A. R. M.).—UNIVERSITY COLLEGE, IBADAN, NIGERIA.]

[*Received, December 10th*, 1956.]

[11] Laidler and Eyring, *Ann. New York Acad. Sci.*, 1940, **39**, 303.
[12] Taft, Purlee, Ritz, and Defazio, *J. Amer. Chem. Soc.*, 1955, **77**, 1587.
[13] Evans, Jones, Jones, and Thomas, *J.*, 1956, 2757.

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720. *Physical Properties and Chemical Constitution. Part XXVI.*[1] *The Dipole Moments of Alkylbenzenes.*

By C. W. N. Cumper, A. I. Vogel, and S. Walker.

The orientation polarisations and dipole moments of seven alkylbenzenes have been calculated from measurements of the dielectric constants and specific volumes of their solutions in benzene. The dipole moments were analysed quantitatively into primary and induced bond moments and these values compared with those of the corresponding alkylpyridines. The dipole moments in benzene solutions are compared with those for the gaseous and liquid states.

Dipole moments of some alkylpyridines have been analysed in terms of their component moments.[1] The same method has now been applied to alkylbenzenes. As the dipole moments are comparatively small (<0·5 D), it is difficult to allow adequately for the distortion polarisation in the alkylbenzene molecules. Any error introduced by this factor will, however, have little effect on the relative dipole moments of the compounds investigated.

Experimental

The apparatus and techniques have been described.[1] Measurements were made in benzene at 25·00° ± 0·01° c.

Materials.—Methyl-, ethyl-, *iso*propyl-, and *tert.*-butyl-benzenes were high-grade commercial products; *sec.*-butylbenzene was a gift from the Koninklijke/Shell-Laboratorium, Amsterdam. *n*-Propylbenzene was prepared here from benzyl chloride, magnesium, and pure ethyl sulphate,[2] and *n*-butylbenzene from benzylsodium and *n*-propyl bromide.[3] Ethyl-, *iso*propyl-, and *tert.*-butyl-benzenes contained traces of sulphur compounds which were removed by repeatedly washing with 10% of their volume of concentrated sulphuric acid until the washings were colourless, then successively with water, 10% sodium carbonate solution, and water. Finally they were dried ($MgSO_4$). Before use, the hydrocarbons were fractionated from sodium two or three times in an all-glass 20 in. column packed with Fenske helices and provided with a variable take-off head, a middle fraction being collected. All the measurements were completed within 24 hr. of the final distillation and the solutions were kept in the dark when not in use. To check their purity the boiling points, densities, and refractive indices of the alkylbenzenes were determined (Table 1) and found to agree satisfactorily with values in the literature.[2, 4, 5]

Table 1.

	B. p.	n_D^{25}	d_4^{25}		B. p.	n_D^{25}	d_4^{25}
Toluene	110·5°	1·4941	0·8622	*n*-Butylbenzene	183°	1·4875	0·8560
Ethylbenzene	136	1·4933	0·8627	*sec.*-Butylbenzene	173	1·4878	0·8580
n-Propylbenzene	159	1·4896	0·8577	*tert.*-Butylbenzene	169	1·4903	0·8624
*iso*Propylbenzene	152	1·4887	0·8577				

Results

Dielectric constants (ε_{12}) and specific volumes (v_{12}) of the solutions in benzene, with weight fractions w_2, are recorded in Table 2. Since the dipole moments of these compounds are small it was necessary to use weight fractions up to 0·1; the simple relation between dielectric constant and weight fraction used previously was extended by the inclusion of a "square" term, *viz.*, $\varepsilon_{12} = \varepsilon_1 (1 + \alpha w_2 + \alpha' w_2^2)$. The specific volumes, over the range studied, were linear functions

[1] Part XXV, Cumper, Vogel, and Walker, *J.*, 1956, 3621.
[2] Vogel, *J.*, 1948, 607.
[3] Vogel, "Practical Organic Chemistry," 3rd Edn., Longmans, London, 1956, p. 934.
[4] National Bureau of Standards, American Petroleum Project 44, NBS Circular C461, United States Government Printing Office, Washing, D.C., 1947.
[5] Forsiati, *J. Res. Nat. Bur. Stand.*, 1950, **44**, 373.

of w_2, *i.e.*, $v_{12} = v_1(1 + \beta w_2)$, and were used in preference to the densities of the solutions, which showed a slight curvature when plotted against w_2. The values obtained for ε_1, α and α' by a method of least squares, and of β, are also given in Table 2.

The total polarisation of the solutes, when extrapolated to infinite dilution $({}_\infty P_2)_2$, were calculated from the values [1] of α and β and are shown in Table 3. The distortion polarisation which is subtracted from ${}_\infty P_2$ to evaluate the orientation polarisation (${}_O P$), was deduced in two ways: (i) it was assumed equal to the molar refraction for sodium light (R_D); (ii) Forsiati's value [5] for the molar refraction (R_∞), obtained by extrapolating the refractive indices of the compound in the visible region to infinite wavelength, was taken as the electron polarisation (${}_E P$) and Altshuller's [6] approximate results for the atom polarisation (${}_A P$) added to ${}_E P$.

TABLE 2.

w_2	v_{12}	ε_{12}	w_2	v_{12}	ε_{12}
	Toluene			*Ethylbenzene*	
0·00156	1·14448	2·2729	0·00194	1·14450	2·2728
0·00295	1·14452	2·2730	0·006165	1·14458	2·2733
0·006526	1·14458	2·2735	0·017770	1·14479	2·2744
0·016224	1·14478	2·2745	0·043021	1·14525	2·2772
0·034326	1·14513	2·2766	0·058059	1·14553	2·2786
0·052271	1·14550	2·2785	0·081610	1·14597	2·2808
0·074698	1·14596	2·2808	0·093062	1·14620	2·2821
$\varepsilon_{12} = 2{\cdot}2726_9(1 + 0{\cdot}0508w_2 - 0{\cdot}039w_2^2)$			$\varepsilon_{12} = 2{\cdot}2725_9(1 + 0{\cdot}0472w_2 - 0{\cdot}030w_2^2)$		
$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0176w_2)$			$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0164w_2)$		
	n-*Propylbenzene*			iso*Propylbenzene*	
0·00164	1·14448	2·2727	0·00170	1·14449	2·2727
0·004928	1·14457	2·2731	0·004883	1·14457	2·2730
0·013662	1·14484	3·2738	0·012780	1·14478	2·2738
0·024591	1·14515	2·2749	0·025478	1·14510	2·2751
0·036116	1·14544	2·2760	0·032970	1·14529	2·2758
0·052027	1·14586	2·2774	0·051908	1·14580	2·2777
0·073837	1·14649	2·2794	0·081837	1·14658	2·2803
			0·096484	1·14694	2·2817
$\varepsilon_{12} = 2{\cdot}2726_9(1 + 0{\cdot}0408w_2 - 0{\cdot}001w_2^2)$			$\varepsilon_{12} = 2{\cdot}2725_4(1 + 0{\cdot}0447w_2 - 0{\cdot}033w_2^2)$		
$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0238w_2)$			$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0225w_2)$		
	n-*Butylbenzene*			sec.-*Butylbenzene*	
0·00165	1·14452	2·2727	0·00244	1·14452	2·2727
0·005990	1·14467	2·2730	0·005357	1·14460	2·2730
0·012219	1·14484	2·2735	0·011211	1·14473	2·2735
0·022230	1·14516	2·2742	0·019898	1·14501	2·2743
0·032528	1·14547	2·2750	0·029075	1·14526	2·2750
0·053750	1·14613	2·2763	0·038538	1·14550	2·2759
0·078502	1·14690	2·2782	0·062476	1·14617	2·2780
0·105359	1·14773	2·2801	0·089103	1·14686	2·2800
$\varepsilon_{12} = 2{\cdot}2726_9(1 + 0{\cdot}0313w_2)$			$\varepsilon_{12} = 2{\cdot}2725_1(1 + 0{\cdot}0397w_2 - 0{\cdot}026w_2^2)$		
$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0274w_2)$			$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0238w_2)$		
	tert.-*Butylbenzene*				
0·00161	1·14448	2·2728	0·029232	1·14506	2·2754
0·005737	1·14457	2·2731	0·054348	1·14555	2·2774
0·010531	1·14466	2·2737	0·071845	1·14590	2·2788
0·020527	1·14487	2·2747	0·087701	1·14620	2·2799
$\varepsilon_{12} = 2{\cdot}2726_2(1 + 0{\cdot}0447w_2 - 0{\cdot}094w_2^2)$			$v_{12} = 1{\cdot}14445(1 + 0{\cdot}0176w_2)$		

The values of R_D, R_∞ (*i.e.*, ${}_E P$), ${}_A P$ and the two values of ${}_O P$ [*viz.*, $({}_\infty P_2 - R_D)$ and $({}_\infty P_2 - R_\infty - {}_A P)$] are also presented in Table 3. It appears that R_D for these compounds includes about 60—70% of their atom polarisations.

The dipole moments were calculated from the usual formula $\mu = 0{\cdot}01281\sqrt{({}_O PT)}$, and are listed under μ_1 (with ${}_O P = {}_\infty P_2 - R_D$) and μ_2 (with ${}_O P = {}_\infty P_2 - R_\infty - {}_A P$) in Table 3. Earlier values (where available) are also given. When complete allowance is made for the atom polarisation, the calculated dipole moments are naturally somewhat smaller (*i.e.*, $\mu_2 < \mu_1$).

[6] Altshuller, *J. Phys. Chem.*, 1954, **58**, 392.

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TABLE 3.

Benzene derivative	$_{\infty}P_2$ (cm.³)	R_D (cm.³)	R_{∞} (cm.³)	$_AP$ (cm.³)	$_0P$ (cm.³) $_{\infty}P_2 - R_D$	$_{\infty}P_2 - R_{\infty} - {}_AP$	μ_1 (D)	μ_2 (D)	μ (calc.) (D)
Methyl	33·96	31·11	29·88 *	1·78 †	2·85	2·30	0·37 ‡	0·34	$0·36_8$
Ethyl	38·92	35·78	34·43 §	2·00	3·14	2·49	0·39	0·35	$0·39_5$
n-Propyl ...	44·04	40·48	39·02	2·22	3·56	2·80	0·42	0·37	$0·42_9$
*iso*Propyl ...	44·18	40·43	39·00	2·22	3·75	2·96	0·43	0·38	$0·42_9$
n-Butyl	48·80	45·11	43·55	2·44	3·69	2·81	0·43	0·37	$0·42_7$
sec.-Butyl ...	49·11	45·05	43·49	2·44	4·06	3·18	0·45	0·39	$0·44_7$
tert.-Butyl...	49·12	45·00	43·45	2·44	4·12	3·23	0·45 ‖	0·40	$0·45_0$

Other literature values: * $(R_{\infty} + {}_AP) = 30·8$.[a] † 2·5,[b] 1·0.[c] ‡ 0·34,[d] 0·39.[e] § $(R_{\infty} + {}_AP) = 35·8$.[a] ‖ 0·53.[d]

[a] Baker and Groves, *J.*, 1939, 1144. [b] McAlpine and Smyth, *J. Amer. Chem. Soc.*, 1933, **55**, 453. [c] Cartwright and Errera, *Proc. Roy. Soc.*, 1936, *A*, **154**, 138. [d] Le Fèvre, Le Fèvre, and Robertson, *J.*, 1935, 480. [e] Tiganik, *Z. phys. Chem.*, 1931, *B*, **13**, 425.

DISCUSSION

Comparison with the Dipole Moments of 4-Alkylpyridines.—The dipole moments of the alkylbenzenes can be expressed by an empirical equation analogous to that suggested for the alkylpyridines, *viz.*,

$$\mu = -\mu_{C-H} + \mu_R + I$$

where μ_{C-H} is the bond moment of hydrogen attached to the benzene ring, I the moment induced in the benzene ring when its hydrogen atom is replaced by the alkyl group R and μ_R the dipole moment associated with the alkyl group itself. μ_R can be expressed in terms of a primary moment "*a*", the C–H bond moment in saturated aliphatic hydrocarbons "*b*", and the moment induced by $(a - b)$ in the C–H bonds (μ_H) and in the other C–C bonds in the substituent chain. The last is assumed to decrease in a geometrical progression with constant ratio "*x*" as the chain-length increases. μ_H will include any moment arising through hyperconjugation with the ring,

e.g.,
$$\mu_R = 3\,\mu_H + (a - b) \text{ for PhMe}$$
$$= 2\,\mu_H + (a - b)(1 + x + x^2) \text{ for PhPr}^n, \text{ etc.}$$

Some variation is possible amongst these parameters but probably the best set (obtained from the dipole moments μ_1, calculated to 0·001D) are: $(a - b) = 0·25$ D, $\mu_{C-H} - I = 0·03_2$ D, $\mu_H = 0·05$ D, and $x = 0·31$. By employing these values the moment shown under μ (calc.) in Table 3, are obtained and the agreement with the measured values supports this method of analysis.

The values of the above parameters can be compared with the corresponding figures for the 4-alkylpyridines [1] [$(a - b) = 0·53$ D, $\mu_H = 0·11$ D, $\mu_{C-H} - I = 0·48$ D, and $x = 0·31$]. x, a property of the side-chain alone, is given the same value in both series and μ_H, as expected, is seen to depend on the value of $(a - b)$.

Since b is thought [7] to be about 0·30 D the primary moment a is about 50% greater in the pyridine than in the benzene series and this, together with the actual magnitude of a (corresponding in the alkylbenzenes to formal electronic charges of $\pm 0·074$ at a distance apart of 1·54 Å) means that part of the electric field polarising the side-chain must reside in the ring system. This field would naturally be greater in a pyridine than in a benzene ring. Cahill and Mueller's approximate wave-mechanical calculations indicate that the moment of the bond from the α-carbon atom of the side-chain to the ring, arising from the different states of hybridisation of the carbon atoms, is only 0·14 D.[8] The magnitudes of a and μ_H

[7] Smith, "Electric Dipole Moments," Butterworths, London, 1955.
[8] Cahill and Mueller, *J. Chem. Phys.*, 1956, **24**, 513.

seem to agree somewhat better with Pullman and Pullman's [9] calculated charge distribution in toluene than with that suggested by Crawford.[10]

Reasons have been advanced for taking μ_{C-H} as 0·40 D in benzene and 0·54 D in pyridine.[1] These are necessarily very approximate, but the change in the moment of the ring itself when an alkyl group is introduced (*i.e.*, *I*) seems to be greater in benzene than in pyridine. This is probable in view of the electron drift towards the nitrogen atom which is already present in the unsubstituted pyridine molecule.

Comparison of the Values for the Dipole Moments of Alkylbenzenes in Benzene Solution with those for the Liquid and the Gaseous State.—In Table 4 the dipole moments of the alkylbenzenes obtained in benzene solutions are compared with Altshuller's values for the pure liquids [6] (the subscripts i and ii refer to the two values assumed previously for the distortion polarisation) and Baker and Groves's [11] moments for the compounds in the gaseous state. On the whole the agreement between the values in solution and in the pure liquid is reasonable, except for *tert.*-butylbenzene where the figure for the pure liquid seems somewhat low, particularly since its moment is less than that reported for *iso*propylbenzene.

The moments in the last two columns of Table 4, $(\mu')_B$ and $(\mu')_L$, are the values of the moments in the gaseous phase calculated by means of Buckingham and Le Fèvre's empirical equations (numbers 3 and 5 in ref. 12) from the experimental moments in benzene solutions and in the liquid state respectively. Except for toluene the agreement with the experimental gas values is less satisfactory than is usually obtained with these equations; the experimental dipole moments in the gaseous phase should be confirmed in order to establish whether the deviations from Buckingham and Le Fèvre's equations are real.

TABLE 4.

	Benzene solution		Liquid		Gas		
Benzene derivative	μ_1	μ_2	μ_1	μ_2	μ	$(\mu_1')_B$	$(\mu_1')_L$
Methyl	0·37	0·34	0·35	0·31	0·37 [a]	0·41	0·39
Ethyl	0·39	0·35	0·40 [b]	0·36	0·58	0·43	0·44
n-Propyl	0·42	0·37	0·40	0·35	—	—	—
*iso*Propyl	0·43	0·38	0·42	0·37	0·65	0·47	0·46
n-Butyl	0·43	0·37	0·42	0·36	—	—	—
sec.-Butyl	0·45	0·39	0·42	0·37	—	—	—
tert.-Butyl	0·45	0·40	0·41	0·36	0·70	0·48	0·44

Other literature values: [a] 0·37, McAlpine and Smyth, *J. Amer. Chem. Soc.*, 1933, **55**, 453; [b] 0·35, van Arkel, Meerburg, and van der Handel, *Rec. Trav. chim.*, 1942, **61**, 767.

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WOOLWICH POLYTECHNIC, LONDON, S.E.18. [*Received, March 29th*, 1957.]

[9] Pullman and Pullman, "Les Théories Electroniques de la Chimie Organique," Masson et Cie., Paris, 1952.
[10] Crawford, *J.*, 1953, 2058.
[11] Baker and Groves, *J.*, 1939, 1144.
[12] Buckingham and Le Fèvre, *J.*, 1952, 1932.

721. *Molecular Polarisability. The Determination of Molecular Anisotropy of Solutes from Scattering of Light by Solutions.*

By R. J. W. Le Fèvre and B. Purnachandra Rao.

Depolarisation factors are measured for solutions in carbon tetrachloride of benzene, naphthalene, phenanthrene, carbon disulphide, chloroform, and acetone. A procedure is developed whereby the " molecular anisotropy " can be computed at infinite dilution. Values of ${}_{\infty}\delta_2{}^2$ so obtained are close to these found for the pure solutes, when these are liquids and when their isothermal compressibilities are available; the new method is advantageous in not requiring information on compressibilities (other than for the solvent) and in being applicable to solid compounds. For the calculation of semi-axes of polarisability from molar Kerr constants which have also been determined in solution, ${}_{\infty}\delta_2{}^2$ is shown to be more appropriate than $\delta_{gas.}{}^2$. Previously-published data on b_1, b_2, and b_3 for chloroform and acetone are amended to 0·673, 0·901, 0·901 and 0·701, 0·684, and 0·482 (all $\times 10^{-23}$) respectively.

Calculation of the semi-axes, b_1, b_2, and b_3, of a molecular polarisability ellipsoid in the general case where $b_1 \neq b_2 \neq b_3$ requires knowledge of at least three physical properties:[1] the molar Kerr constant (${}_mK$), the electronic polarisation (${}_EP$), and the molecular anisotropy (δ^2). Relevant equations are given as (1) to (3) (symbols have the meanings stated in ref. 1):

$$ {}_mK = 2\pi N(\theta_1 + \theta_2)/9 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1) $$

$$ {}_EP = 4\pi N(b_1 + b_2 + b_3)/9 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2) $$

$$ \delta^2 = [(b_1 - b_2)^2 + (b_2 - b_3)^2 + (b_3 - b_1)^2]/(b_1 + b_2 + b_3)^2 \quad . \quad . \quad (3) $$

From the molar Kerr constant of a substance the sum $(\theta_1 + \theta_2)$ of the " anisotropy " and the " dipole " terms respectively is obtained directly by eqn. (1); separation of θ_1 from θ_2 is effected through equations (2) and (3) to compute θ_1:

$$ \theta_1 = ({}_DP/45kT \cdot {}_EP)[(b_1 - b_2)^2 + (b_2 - b_3)^2 + (b_3 - b_1)^2] \quad . \quad . \quad (4) $$

θ_2 follows by difference:

$$ \theta_2 = [(\mu_1{}^2 - \mu_2{}^2)(b_1 - b_2) + (\mu_2{}^2 - \mu_3{}^2)(b_2 - b_3) + (\mu_3{}^2 - \mu_1{}^2)(b_3 - b_1)]/45k^2T^2 $$
$$. \quad . \quad . \quad . \quad . \quad . \quad (5) $$

The desired semi-axes can then be evaluated from eqns. (2), (4), and (5). Relation (3) is thus of vital importance in all applications of the Kerr effect to problems of molecular structure.

The quantity δ^2 is drawn from experiment by eqn. (6):

$$ \delta^2 = 10\Delta/(6 - 7\Delta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6) $$

where Δ is the " depolarisation factor " for light scattered transversely by the material when an unpolarised ray passes through it; Δ is defined as the ratio of the intensities of the light polarised in a horizontal plane (*i.e.*, the plane of the incident and scattered beams) to that polarised in a vertical plane.[2,3] Actually eqn. (6) is valid only for scattering by gases. For liquids and dense media cognisance has to be taken of the fluctuations in the number of molecules in an element of volume V; these are given by $\overline{(\Delta\nu)^2} = RT\beta\nu^2/NV$, where $\overline{(\Delta\nu)^2}$ is the mean square of the deviation of the number of molecules per unit volume

[1] Le Fèvre and Le Fèvre, *J.*, 1953, 4041, 1954, 1577; *Rev. Pure Appl. Chem.*, 1955, **5**, 261.
[2] Cabannes, " La Diffusion Moléculaire de la Lumière," Les Preoses Universitaires de France, Paris, 1929.
[3] Bhagavantam, " Scattering of Light and the Raman Effect," Andhra University, Waltair, 1940.

from the mean value v; β is the isothermal compressibility. Consequently, for liquids, eqn. (7) should be used instead of (6):

$$\delta^2 = 10RT\beta v\Delta/(6 - 7\Delta)N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Unfortunately the literature contains depolarisation data for only a few dozen compounds. When the same substance has been examined in the liquid and the vapour state, δ^2 from (7), with use of $\Delta_{liq.}$ and β, and δ^2 from (6), with use of Δ_{gas}, have usually [2,3] not been the same, $\delta_{gas}{}^2$ always exceeding $\delta_{liq.}{}^2$.

Since we are using extensively molar Kerr constants ${}_\infty({}_mK_2)$ determined at infinite dilution in carbon tetrachloride and other solvents, and because many interesting substances are ordinarily solid and information on the isothermal compressibility of their melts is wholly lacking, the present work was initiated to enquire (*a*) whether δ^2 for a solute can be obtained directly from observations on a series of solutions, and (*b*) which, of $\delta_{gas}{}^2$ or $\delta_{liq.}{}^2$, is the more appropriate for the calculation of θ_1 in ${}_\infty({}_mK_2)$.

Experimental

Depolarisation factors Δ were measured at *ca.* 20° by the Cornu method.[2,3] Light from a 1000 w projection lamp was condensed on a 2 × 2 mm. square opening, acting as a source, situated close to the focus of a variable-aperture camera lens (f = *ca.* 30 cm.), mounted on the wall of a dark cabin inside which was an optical bench carrying a 50 c.c. spherical flask serving as the cell (this was painted black externally save for three small clear circles of *ca.* 1 cm. diameter for the incident and scattered beams), a Wollaston double-image prism, and a Nicol prism and circular scale readable to 0·01°. Mixtures were prepared by weight and concentrations recorded as molar fractions, f_2. Freedom from dust and other particles was secured by distillation as described in refs. 1 and 2 or by filtration through sintered-glass diaphragms. The latter method was particularly explored because it was the only technique which could be applied to solutions of solid solutes; it did not produce such clear liquids as did the former, but provided that the solvent was similarly treated the *changes* in Δ from solvent to solutions were not significantly affected. The last point, which is essential to what follows, was exhaustively checked by experiments on systems in which both solvent and solute were easily volatile so that both methods could be used. In cases where fluorescence was suspected the incident light was first passed through aqueous quinine sulphate (3·6 g./100 c.c.) slightly acidified with sulphuric acid. Convergence corrections and other practical details were as described by Bhagavantam.[3] If the two images seen through the Nicol–Wollaston combination were equally illuminated when the analyser made an angle ϕ with the horizontal, then Δ = (intensity of horizontally polarised component) ÷ (intensity of vertically polarised component) = $\tan^2\phi$. Inversion of the Wollaston prism did not affect the readings of ϕ (cf. Volkmann [4]).

Carbon tetrachloride, used as solvent, was from a sulphur-free bulk supply which had been fractionated through a 1 m. column packed with glass helices. It was stored over calcium chloride and redistilled immediately before use. The solutes were purified by distillation or recrystallisation as appropriate.

Results.—The apparatus and technique were checked by making a number of determinations on five samples of redistilled sodium-dried benzene. Values of 100Δ fell between 40·1 and 41·0 (mean 40·6) with a standard error of $\pm$0·2. Such a figure compares satisfactorily with others.[2,3] In the case of carbon tetrachloride, purified as in the previous paragraph, however, 100Δ has been consistently found to lie within the limits 3·29 and 3·52, *i.e.*, lower than any earlier results (Cabannes [2] cites 4·45, 5·6, 6·1, 10·6, and 11·0 from various authors; Bhagavantam [3] gives 6·0). It is possible that this difference can be explained by improvements, especially in distillation, introduced during the past 20 years in large-scale industrial manufacture, since older specimens and samples of "technical" grade have been found to give values of 100Δ of the order of those in the literature. For the material used in this work a mean value of $10^2\Delta_1$ = 3·46 $\pm$ 0·04, from five separate preparations, was adopted.

Table 1 lists the depolarisation factors measured for solutions of six solutes in carbon tetrachloride. Subscripts 1, 2, and 12 denote solvent, solute, and solution respectively.

[4] Volkmann, *Ann. Physik*, 1935, **24**, 457.

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Molecular Anisotropy at Infinite Dilution.—Depolarisation factors of binary mixtures have been reported before,[5, 6, 7] but never with the present objective of obtaining the molecular anisotropy of a solute at infinite dilution, ${}_{\infty}\delta_2^2$. The procedure now adopted may be outlined as follows: Equation (7) is rewritten for a solution containing a molar fraction f_2 of solute of molecular weight M_2 in a solvent of molecular weight M_1:

$$\delta_{12}^2 = 10\Delta_{12}\boldsymbol{R}T\beta_{12}d_{12}/(6 - 7\Delta_{12})M_{12} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where $\boldsymbol{R} = 0{\cdot}8314 \times 10^8$ ergs/deg., T is the absolute temperature, and d is the density. The experimental values of Δ_{12} in Table 1 when plotted against f_2 form smooth curves which, near

TABLE 1. *Depolarisation factors for solutes in carbon tetrachloride.*

Benzene		$C_{10}H_8$		Phenanthrene		CS_2		$CHCl_3$		Me_2CO	
10^5f_2	$10^3\Delta_{12}$	10^5f_2	$10^3\Delta_{12}$	10^5f_2	$10^3\Delta_{12}$	10^5f_2	$10^3\Delta_{12}$	10^5f_2	$10^3\Delta_{12}$	10^5f_2	$10^3\Delta_{12}$
4742	6·30	1331	5·49	533	4·566	2021	7·13	1853	4·03	2206	5·13
9816	9·48	2134	6·73	1037	5·459	3686	12·34	3549	4·73	5755	5·99
13,993	13·44	3507	8·73	2042	6·863	6243	18·43	5144	5·51	9487	6·98
17,770	15·51	5022	10·03	2512	7·666	8336	22·21	7085	6·50	13,209	8·41
19,833	16·28			3877	10·470	10,774	30·59	9626	7·01	16,670	9·30
22,506	18·46					13,312	33·40	12,063	8·50	20,215	9·50
						16,181	38·55	15,040	9·70		
						20,783	39·91	19,287	12·56		

infinite dilution, can be taken as rectilinear (eqn. 9). A corresponding treatment has often been given [8] to densities (eqn. 10); a similar relation will be assumed for the compressibility of a solution (eqn. 11).

$$\Delta_{12} = \Delta_1 + Af_2 \quad . \quad . \quad . \quad (9) \qquad \beta_{12} = \beta_1 + Bf_2 \quad . \quad . \quad . \quad (11)$$

$$d_{12} = d_1 + Df_2 \quad . \quad . \quad . \quad (10) \qquad M_{12} = M_1f_1 + M_2f_2 \quad . \quad (12)$$

Equation (8) is expanded, by substitution from equations (9) to (12), and differentiated with respect to f_2. When $f_2 = 0$ equation (13) is obtained.

$${}_{\infty}\delta_2^2 = \delta_1^2\left[1 + \frac{A}{\Delta_1} + \frac{B}{\beta_1} + \frac{D}{d_1} + \frac{(M_1 - M_2)}{M_1} + \frac{7A}{(6 - 7\Delta_1)}\right] \quad . \quad . \quad . \quad (13)$$

In practice, equation (9) is not used as such, but values of $\Delta\Delta_{12} = \Delta_{12} - \Delta_1$ are fitted by least squares to (14), whence A follows as the coefficient of f_2.

$$(\Delta\Delta_{12})f_2 = Af_2 + (\text{constant})f_2^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

D can also be found by an expression analogous to (14); often it is adequately computed by eqn. (15):

$$D = \Sigma(\Delta d)/\Sigma f_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

The constant B in an equation of type (11) presents some difficulty since unfortunately isothermal compressibilities of solutions as functions of concentration seem to have been little studied. An idea of the order of magnitude of B is obtained from the β's for pure liquids published by Freyer, Hubbard, and Andrews; [9] B should be roughly $\beta_2 - \beta_1$, *e.g.*, for the system benzene–carbon tetrachloride, *ca.* $-9{\cdot}7 \times 10^{-12}$, so that $B/\beta_1 = -9{\cdot}7/103{\cdot}4 = \sim 0{\cdot}094$. Parthasarathy [10] has examined the adiabatic compressibilities of a few mixtures, including that just mentioned; from his results $(\beta_{12} - \beta_1)_{\text{adiab.}}/f_2\beta_1 = -0{\cdot}046$. By either estimate B/β_1 is small, and, especially in view of the magnitudes of A/Δ_1 which enter (13), may safely be ignored.

Table 2 lists information, from Table 1, leading to ${}_{\infty}\delta_2^2$ for the various solutes in carbon tetrachloride, δ_1^2 for which is $1{\cdot}569 \times 10^{-3}$ at 20°, when d_4^{20} is 1·5940 and β_1 is $103{\cdot}43 \times 10^{-12}$.

[5] Rav, *Proc. Indian Ass. Cultivation Sci.*, 1925, **9**, 19.
[6] Parthasarathy, *Indian J. Phys.*, 1934, **8**, 275.
[7] Kremann and Gastinger, *Akad. Wiss. Wien*, 1938, **2**, *B*, **147**, 52.
[8] Le Fèvre, " Dipole Moments," Methuen, London, 3rd edn., 1953, p. 56.
[9] Freyer, Hubbard, and Andrews, *J. Amer. Chem. Soc.*, 1929, **51**, 759.
[10] Parthasarathy, *Proc. Indian Acad. Sci.*, 1936, **3**, 297.

Discussion.—Benzene and the last three compounds in Table 2 have been studied in both the liquid and the vapour state by several previous workers (see refs. 2 and 3). In Table 3 values of $\delta_{liq.}^2$ and δ_{gas}^2, taken from refs. 2 and 3, and multiplied by 2 to conform to equations (6), (7), (8), and (13), are compared with ${}_\infty\delta_2^2$ now found. It is seen that

TABLE 2. *Calculation of molecular anisotropies of solutes at infinite dilution.*

Solute	Right-hand side of eqn. (14)	D	$10^3\ {}_\infty\delta_2^2$
Benzene	$0{\cdot}657f_2 + 0{\cdot}046f_2^2$	−0·5997	32·8
Naphthalene	$1{\cdot}686f_2 - 7{\cdot}07f_2^2$	−0·6749	80·9
Phenanthrene	$1{\cdot}666f_2 + 3{\cdot}05f_2f_2$	−0·6671	79·4
Carbon disulphide	$2{\cdot}879f_2 - 5{\cdot}08f_2^2$	−0·4286	137·9
Chloroform	$0{\cdot}332f_2 + 0{\cdot}680f_2^2$	−0·0899	17·5
Acetone	$0{\cdot}502f_2 - 0{\cdot}989f_2^2$	−0·6285	25·6

TABLE 3. *Values of* $\delta_{liq.}^2$, δ_{gas}^2, *and* ${}_\infty\delta_2^2$.

	$10^3\ \delta_{liq.}^2$	$10^3\ \delta_{gas}^2$	$10^3\ {}_\infty\delta_2^2$
Benzene	36·0	79·2	32·8
Carbon disulphide	145	221	138
Chloroform	18·6	30·6	17·5
Acetone	25·4	27·3	25·6

equation (13) leads to molecular anisotropies which are close to those calculated from $\Delta_{liq.}$, $\beta_{isothermal}$, etc. Eqn. (13) therefore offers the practical advantage that ${}_\infty\delta_2^2$ becomes accessible for the many solid and other substances for which isothermal compressibilities are unknown.

There remains the question which, of ${}_\infty\delta_2^2$ (or $\delta_{liq.}^2$) or δ_{gas}^2, is the more appropriate for use in calculating θ_1 from a molar Kerr constant determined at infinite dilution in a solvent. Table 4 gives the results of estimating δ^2 by equations (1), (2), and (3) in the

TABLE 4. *Values of* ${}_\infty\delta_2^2$ *calculated from* ${}_\infty({}_mK_2)$ *and by eqn.* (13).

Solute	$10^{12}\ {}_\infty({}_mK_2)$	${}_EP$ (c.c.)	$10^3\ {}_\infty\delta_2^2$ from ${}_\infty({}_mK_2)$	$10^3\ {}_\infty\delta_2^2$ by eqn. (13)
Benzene	7·24 [a]	25·1 [a]	34·8	32·8
Naphthalene	48·1 [b]	41·8 [b]	85·7	80·9
Phenanthrene	82·6 [c]	56·9 [d]	72·2	79·4
Carbon disulphide	27·8 [c]	20·4 [c]	191	138

[a] From ref. 1. [b] From ref. 11. [c] From unpublished work. [d] Estimated by taking ${}_DP/{}_EP$ as 1·1. [e] From ref. 12.

cases of four non-polar solutes, for each of which $\theta_2 = 0$ in eqn. (1). With benzene, naphthalene, and phenanthrene it is clear that ${}_\infty\delta_2^2$ is adequate for the purpose mentioned. With carbon disulphide, an anisotropy about midway between ${}_\infty\delta_2^2$ or $\delta_{liq.}^2$ and δ_{gas}^2 seems to be required—a fact for which we have no explanation at present. Fortunately, in practice eqn. (13) will be needed during the extraction of b_1, b_2, and b_3 for a polar molecule, whose θ_2 is likely greatly to exceed θ_1, so that high precision in θ_1 will not be essential (cf. pyridine and quinoline [13]).

TABLE 5. *Values of* δ^2 *calculated from semi-axes already published.*

Molecule	Ref.	$10^{24}b_1$	$10^{24}b_2$	$10^{24}b_3$	$10^3\delta_2^2$
Benzene	1	1·114	1·114	0·733	33·1
Naphthalene	11	2·15	1·76	1·03	79·5
Chloroform *	1	0·673	0·901	0·901	17·0

* The semi-axes for chloroform are incorrectly given in Tables 7 and 8 of *J.*, 1953, 4041. They should read as above with CCl_4 as solvent, and as 0·665, 0·904, 0·904 respectively with C_6H_6 as solvent.

Reference is made in Table 5 to three substances whose polarisability ellipsoids have been derived in past papers without recourse to depolarisation data. As a check values of

[11] Le Fèvre and Le Fèvre, *J.*, 1955, 1641.
[12] Le Fèvre and Rao, *Austral. J. Chem.*, 1954, **7**, 135.
[13] Le Fèvre and Le Fèvre, *J.*, 1955, 2750.

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δ^2 are evaluated directly, by eqn. (3), from the semi-axes. Agreement is reassuring, especially for naphthalene since in this instance Le Fèvre and Le Fèvre [11] used refractive indices of the crystal to compute b_1, b_2, and b_3.

Finally, the analysis of acetone, given in *J.*, 1953, 4041, involved δ_{gas}^2. In view of the conclusions now reached a more appropriate figure is ${}_{\infty}\delta_2^2 = 0{\cdot}0256$; when this is used the semi-axes, b_1, b_2, and b_3 appear as 0·701, 0·684, and 0·482 (all $\times 10^{-23}$) cm. respectively.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, April 2nd,* 1957.]

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722. *Photo- and Semi-conductance in Organic Crystals. Part III.*[1,2] *Photoeffects in Dry Air with Eleven Organic Compounds.*

By L. E. LYONS and G. C. MORRIS.

Photocurrents between 10^{-10} and 10^{-16} A in dry air were detected in single crystals of several aromatic organic substances which have a very high dark resistivity. Surface and bulk currents, I_S and I_B, were distinguished in anthracene which was considered typical. The dependence of I_S and I_B upon voltage, wavelength, time, light intensity, and area of illumination is reported. Space charges were found both at electrodes and over the area of a light beam shining between the electrodes. The quantum efficiency both of carrier liberation inside the crystal and of electron production in the outer circuit, the surface and bulk mobilities, and the mean free path are estimated. The mechanism of carrier liberation and the influence of surface double layers are discussed. It is suggested that both electrons and positive holes are trapped. A theory is advanced to explain the spectral dependence of I_B. The magnitude of the photocurrents is correlated with a number of other properties of the substances.

REFERENCES to earlier work on photo- and semi-conduction in organic crystals were given in Parts I and II.[1,2] Since then much further work has appeared on photoeffects [3-9] and on semiconduction [5,10-13] in hydrocarbon crystals as well as much work on dye crystals.[14-16] Most of the hydrocarbon work has been done on anthracene, but the semiconduction of some solid solutions has been studied [10] and a brief mention has been made of a photoeffect in chrysene.[8]

This paper is concerned with the photoeffects in a range of hydrocarbon and related molecules, few of which have been reported previously as photoconductors, except in our preliminary publication.[9] Anthracene has also been studied further. The spectral dependence of the photocurrent is mentioned here only for anthracene: other substances

[1] Part I, Bree, Carswell, and Lyons, *J.*, 1955, 1728.
[2] Part II, Carswell and Lyons, *J.*, 1955, 1734.
[3] Zinszer, *Z. Naturforsch.*, 1956, **11a**, 306.
[4] Goldsmith, Ph.D. Thesis, Purdue, 1955.
[5] Inokuchi, *Bull. Chem. Soc. Japan*, 1956, **29**, 13.
[6] Schneider and Waddington, *J. Chem. Phys.*, 1956, **25**, 358.
[7] Bree and Lyons, *ibid.*, 1956, **25**, 384, 1284.
[8] Northrop and Simpson, *Proc. Phys. Soc.*, 1955, **68**, 974.
[9] Lyons and Morris, *ibid.*, 1956, **69**, 1162.
[10] Northrop and Simpson, *Proc. Roy. Soc.*, 1956, **234**, *A*, 124, 136.
[11] Many, Harnik, and Gerlich, *J. Chem. Phys.*, 1955, **23**, 1733.
[12] Pick and Wissman, *Z. Physik*, 1954, **138**, 436.
[13] Eley and Parfitt, *Trans. Faraday Soc.*, 1955, **51**, 1529.
[14] Vartanyan, *Doklady Akad. Nauk S.S.S.R.*, 1954, **94**, 829; *Zhur. fiz. Khim.*, 1953, **27**, 272; 1954, **8**, 856.
[15] Weigl, *J. Chem. Phys.*, 1956, **24**, 364, 577, 883.
[16] Nelson, *ibid.*, 1955, **23**, 1550; *J. Opt. Soc. Amer.*, 1956, **46**, 10.

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will be discussed in a later paper. All behaved in general similarly to anthracene. We now report the dependence of the D.C. photocurrent on applied voltage, light intensity, electrode contacts, and area and time of illumination for single crystals in dry air. Both surface and bulk photocurrents were obtained. Anthracene, naphthalene, phenanthrene, chrysene, 1 : 2-benzanthracene, 1 : 2-5 : 6-dibenzanthracene, diphenyl, *p*-terphenyl, dibenzothiophen, and acridine all gave photocurrents. No current was obtained with hexamethylbenzene or 1 : 2 : 3 : 4 : 5 : 6 : 7 : 12 : 13 : 16-decahydropyrene.

Experimental

The D.C. amplifier [17] built around a Mullard ME1402 electrometer valve could detect less than 10^{-16} A. Current gain was 10^6, hysteresis effects were absent, and the time constant was 2 sec. (for a 10^{11} ohm resistor) corresponding to the galvanometer period. The amplifier was calibrated for a grid voltage change of $\pm 1{\cdot}5$ v, being over the range $\pm 0{\cdot}25$ v. Random noise fluctuations corresponded to changes in grid bias of 100 μv. The field applied to the crystal could be reversed. For the surface currents the " Alkadag " electrodes were connected to platinum wires mounted on a polystyrene support. Often the crystal was held only by the electrode leads but sometimes a silica disc was used as a support. Phosphoric oxide was used as desiccant since water vapour decreased the photocurrent. For currents through the bulk crystal a semitransparent aluminium surface provided one electrode. Light from a tungsten, mercury, or hydrogen lamp was polarized by a Wollaston prism after passing through the monochromator of a Beckman spectrophotometer; the electric vector of the light was made to lie along a crystal optical direction. The mercury lamp was calibrated by a Schwarz linear thermopile, and the other lamps were compared with the mercury lamp by means of an IP28 photomultiplier.

Anthracene, chrysene, diphenyl, *p*-terphenyl, acridine, and dibenzothiophen were purified by chromatography on aluminium oxide with light petroleum in a darkened room; for pyrene, see ref. 18. Naphthalene, purified with the aid of a Raney nickel catalyst, was kindly supplied by Mr. R. Redies. Phenanthrene was purified as described previously,[19] and the benzanthracenes by sublimation. Fluorescence measurements above 4000 Å on all substances except naphthalene recorded no peaks other than those reported in the literature.[20] Single crystals of the hydrocarbons were obtained by sublimation in an inert atmosphere, and those showing a twinning plane, obtained frequently with pyrene and phenanthrene, were discarded. The (001) face was that commonly developed but with 1 : 2-5 : 6-dibenzanthracene the (010) face appeared. Relatively large crystals (1 cm. $\times$ 1 cm. $\times$ 10 μ) were obtained with diphenyl and naphthalene, but most of the crystals were about 3 mm $\times$ 3 mm $\times$ 5 μ. As the heterocyclic substances gave needles on sublimation, a mass of similarly oriented single crystals was used. All crystals were examined under a polarizing microscope for the identification of the optical directions, and those with visible flaws were rejected. Thicknesses were measured with an Ehringhaus compensator. Results with sandwich cells were confined to anthracene, which was the only substance available in a suitable form.

Results

Current–Time Relation.—When other factors (*e.g.*, field, light intensity) are held constant the *I–t* (current–time) relation may be studied during the first fraction of a second, during the first minute, or during an hour or longer. Our equipment allowed us to study the last two cases, but a study during the first fraction of a second has recently been reported by Goldsmith [4] who found a build-up time for anthracene of about 10^{-5} sec.

With the surface cell the rise of I_S (surface currect) to a maximum, I_p, in *ca.* 2 sec., followed by a fall to an approximately constant value, I_e, was obtained either with uneven illumination over the surface of the crystal (discussed below) or with bad electrode contacts (confirming the results of others [3]). If a crack developed in the crystal near an electrode, the maximum was obtained. The occurrence of a maximum, whatever its cause, was always accompanied by the possibility of obtaining a back-photocurrent, I_b, *i.e.*, a current in the opposite direction

[17] Barth, *Z. Physik*, 1934, **87**, 399; Penick, *Rev. Sci. Instr.*, 1935, **6**, 115.
[18] Levy and Campbell, *J.*, 1939, 1442.
[19] Carswell and Iredale, *Austral. J. Appl. Sci.*, 1953, **4**, 329.
[20] Sangster and Irvine, *J. Chem. Phys.*, 1956, **24**, 670.

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to the original, when the field was switched off or decreased and the crystal re-illuminated. This result [21] is ascribed to the build-up of space charge in the crystal. The measure of the back-photocurrent under uniform illumination indicated the quality of the electrode contacts. Fig. 1 shows I_B–t curves with bad electrode contacts and the effect of remaking a bad contact; other substances behave similarly.

When the light is switched off but the field remains on, I_B decays in two stages, an initial one where the decay is too fast to measure, and a slow final one, covering the last 10%, where the decay followed a first-order law with a constant $k = 0{\cdot}04$ sec.$^{-1}$. This slow stage only

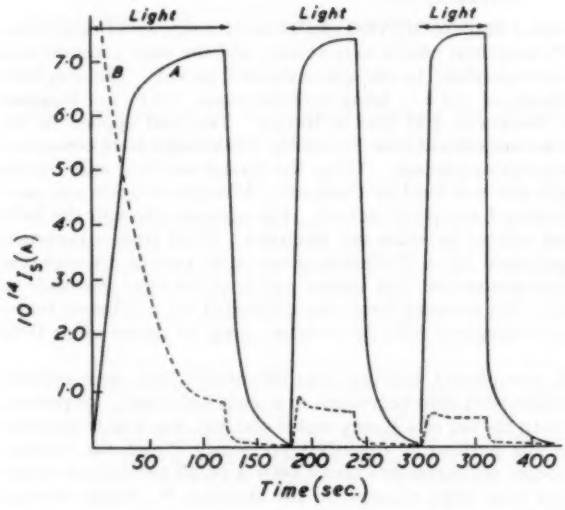


FIG. 1a. *Effect of remaking a bad contact with an anthracene crystal (4 mm. × 2 mm. × 5 μ) at a field strength of 500 v cm.$^{-1}$ and light intensity of 10^{16} quanta sec.$^{-1}$ cm.$^{-2}$.* *A*, Good contact; *B*, bad contact.

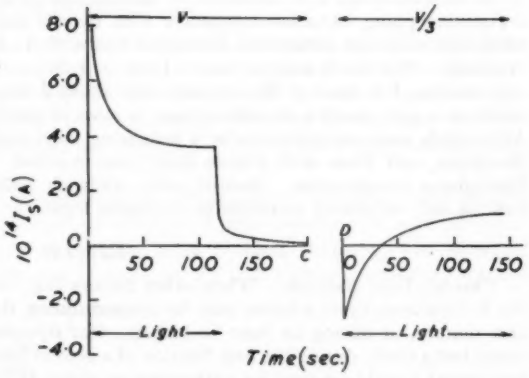


FIG. 1b. *Evidence of space charge in an anthracene crystal (5 mm. × 1 mm. × 4 μ) with bad contacts at a field strength of 1000 v cm.$^{-1}$ and light intensity of 10^{16} quanta sec.$^{-1}$ cm.$^{-2}$.*

Between C and D an interval of 7 min. was allowed for decay of capacitative coupling effects in the circuit caused by altering the potential.

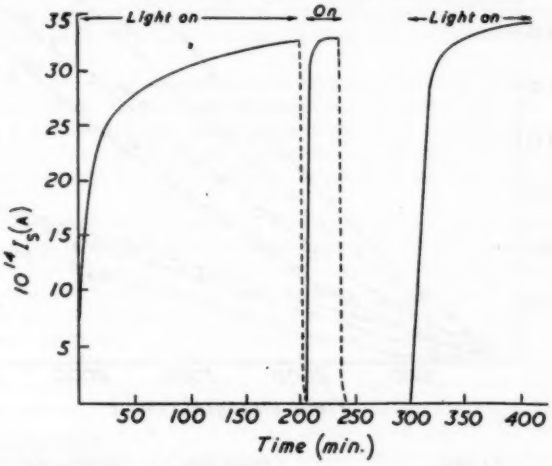
occurred when faulty electrode contacts were present, and the fact that it was due to faulty contacts was illustrated by deliberately introducing such faults, whereupon the decay from I_p to I_e followed first-order kinetics for about 30 sec. with a constant $k_1 = 0{\cdot}11$ ($\pm 0{\cdot}02$) sec.$^{-1}$, and thereafter a first-order decay occurred with the same constant $k_2 = 0{\cdot}04$ ($\pm 0{\cdot}01$) sec.$^{-1}$. Both k_1 and k_2 were independent of V (field strength), L (light intensity) and λ (wavelength).

The decay of I_b was also of the first order with a constant $k_b = 0{\cdot}06$ ($\pm 0{\cdot}01$) sec.$^{-1}$ at $L = 10^{16}$ quanta sec.$^{-1}$ cm.$^{-2}$; k_b was independent of V and λ but increased as L increased. The production and the decay of the back-photocurrent I_b were studied as a function of λ

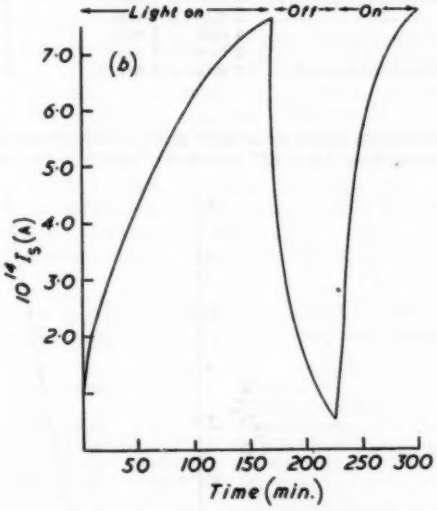
[21] Chynoweth and Schneider, *J. Chem. Phys.*, 1954, **22**, 1021.

(wavelength), all wavelengths in the absorption region being effective. Once the back-photocurrent had been produced and allowed to decay completely, it could not be re-created, even by use of light of shorter wavelength. For example, if I_b was thus completely " eliminated " by light of λ 4039 Å, then subsequent illumination at shorter wavelengths (*e.g.*, 3650 Å) gave no

FIG. 2. *Plot of surface current against time for a long interval.*



(*a*) 1 : 2-5 : 6-Dibenzanthracene (crystal 1·5 mm. × 1 mm. × 2 μ). Field strength 1000 v cm.$^{-1}$, light intensity 1·4 × 10^{13} quanta sec.$^{-1}$ cm.$^{-2}$ at 3650 Å.

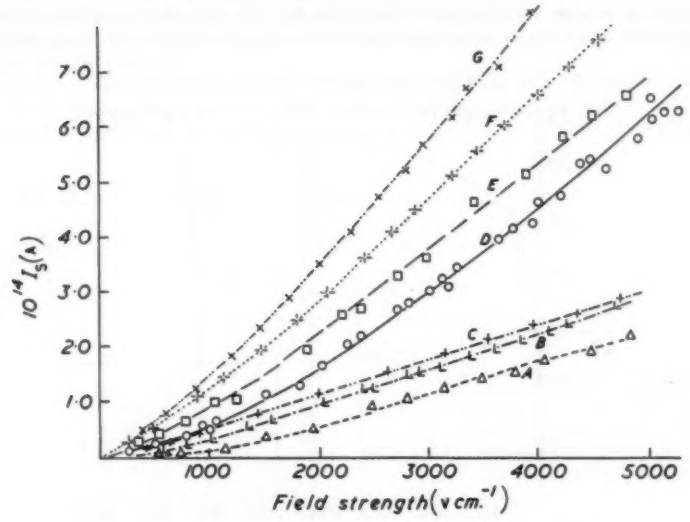


(*b*) Phenanthrene (crystal 3 mm. × 1 mm. × 1 μ). Field strength 2000 v cm.$^{-1}$, light intensity 3 × 10^{14} quanta sec.$^{-1}$ cm.$^{-2}$, polychromatic at wavelengths greater than 3000 Å.

further I_b. This contrasts with a previous result,[3] but this is understandable if I_b in that case had not been completely eliminated in the first illumination. Irrespective of the wavelengths (4100—2600 Å) used to create the space-charge responsible for I_b, any wavelength in the same range was effective in eliminating it.

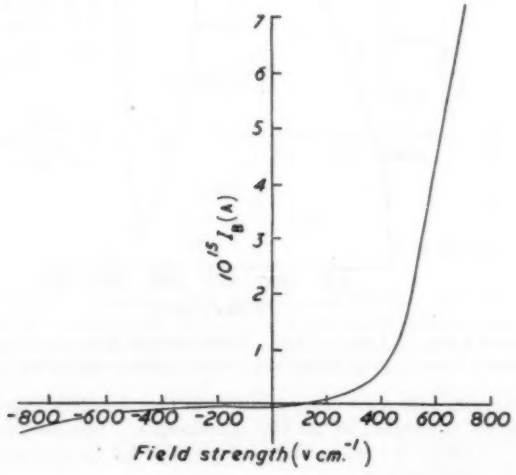
Over longer periods, I_S increased steadily with every substance (see Fig. 2). A similar

FIG. 3a. *Surface current–field strength curves.*



Crystal	Crystal size	Light intensity (quanta sec.$^{-1}$ cm.$^{-2}$)
A *p*-Terphenyl	2 mm. × 1 mm.	6×10^{14}
B Phenanthrene	2 mm. × 1 mm.	4×10^{13}
C Naphthalene	5 mm. × 1 mm.	4×10^{13}
D Chrysene	2 mm. × 1 mm.	2×10^{12}
E Anthracene	4 mm. × 1 mm.	2×10^{10}
F Pyrene	3 mm. × 1 mm.	6×10^{12}
G 1 : 2-5 : 6-Dibenzanthracene ...	2 mm. × 1 mm.	6×10^{11}

FIG. 3b. *Bulk current–field strength curves for an anthracene crystal* (10 *mm.* × 10 *mm.* × 5 *mm.*) *with a light intensity of* $1{\cdot}4 \times 10^{13}$ *quanta sec.*$^{-1}$ *cm.*$^{-2}$ *on one electrode.*



result has been observed with tetracene,[1] anthracene,[21] rhodamine B, and crystal-violet.[14, 15] When the light was switched off, I_S fell almost to zero rapidly (Fig. 2*a*), except with phenanthrene (Fig. 2*b*). Re-illumination within a short time (Fig. 1*a*) restored I_S to the value obtained just before switching off. A longer interval lengthened the time of the second build-up. Field-free illumination lowered the subsequent build-up time. It is important that if the field direction were reversed at any time of this build-up, the current was much smaller, but gradually increased, thus indicating that the electrodes were being polarized (double layer). Because of the gradual increase in I_S with time, a standard time of three minutes was used in the other experiments to be described.

With the sandwich cell, the peak current was always followed by a drop to a steady value. For a crystal 5 mm. thick, no back-photocurrent was detected with the positive electrode illuminated unless a very high light intensity was used. For a thin sublimation flake, I_b was about one-twentieth of I_c when the positive electrode was illuminated and about one-fifteenth when the negative electrode was illuminated. In such cases, the electrode contacts were deemed satisfactory.

Current–Field Strength Relation.—Some I_S–V curves (where V is the ratio of applied voltage to electrode separation) in the literature show straight lines for tetracene and anthracene,[1, 5, 21] but other workers [3, 4] have found that, for anthracene, the curve bends towards the current axis with increasing voltage. After a very large number of surface-cell experiments on many crystals of each substance the results in Fig. 3 were established as representative. There is a slight upward trend most noticeable at comparatively low field strengths. In the case of *p*-terphenyl, the curvature was more pronounced. Experimental precautions observed included taking the points at the various voltages in a nearly random order (*e.g.*, for chrysene the order of points shown in Fig. 3*a*, with increasing field strength was 8, 4, 24, 9, 5, 25, 10, 6, 23, 11, 26, 22, 12, 27, 21, 3, 13, 20, 28, 7, 14, 19, 15, 29, 18, 2, 16, 30, 17, 1), reversing the direction of the field on each crystal and repeating the observations, and the use only of crystals in which I_b was negligible and the electrode contacts therefore satisfactory. Failure to observe the last precaution and to neutralize the resultant space charge produced curves which bent towards the voltage axis. The shape of the curves was independent of the polarization of the light (in the range of Table 1) and its intensity.

With a sandwich cell the direction of the field made a great difference to the plot of bulk current against field strength in agreement with previous work; [3, 21] see Fig. 3*b*.

The field direction in the (001) plane made no difference to the surface current, as was shown by experiments on the one crystal with four electrodes.

Current–Light Intensity Relation.—Plots of surface current against light intensity for four substances in the surface cell are shown in Fig. 4. The linear relation between I_S and L reported earlier for anthracene [1, 21] holds for light intensities less than $1{\cdot}6 \times 10^{13}$ quanta sec.$^{-1}$ cm.$^{-1}$. The shape of the curves was independent of the polarization of the light, wavelength (in range of Table 1) and field strength. Goldsmith,[4] who varied L over a 100-fold range, reported a tendency to saturation, but this did not occur in our experiments over a wider range.

TABLE 1. *Ratio of number of electrons in external circuit to number of quanta absorbed, at an applied voltage of* 1 V *cm.*$^{-1}$ *with uniform illumination in the surface cell.*

Crystal	Range (Å)	Ratio	Crystal	Range (Å)	Ratio
Anthracene	3300—3920	10^{-7}	Acridine	3500—4000	10^{-9}
1 : 2-5 : 6-Dibenzanthracene	3000—4000	2×10^{-8}	Dibenzothiophen	3000—4000	5×10^{-10}
1 : 2-Benzanthracene	3000—3800	5×10^{-9}	Phenanthrene	2600—3130	3×10^{-10}
Chrysene	3000—3650	4×10^{-9}	Naphthalene	2600—3130	5×10^{-11}
Pyrene	3000—3650	10^{-9}	*p*-Terphenyl	2600—3100	3×10^{-12}
			Diphenyl	2600—2800	10^{-12}

The order of magnitude of the currents obtained with a known number of quanta may be seen from Table 1 where each result represents an average over the wavelength range stated.

The only ratio of current to quanta observed previously [2] (on anthracene, 5×10^{-7} electrons/quantum) was in reasonable agreement with the above.

With the sandwich cell, the curve of bulk current against intensity depended on whether the illuminated electrode was positive or negative. When it was positive, the current was proportional to L, and when negative it was proportional to $L^{\frac{1}{2}}$. L was varied from zero to

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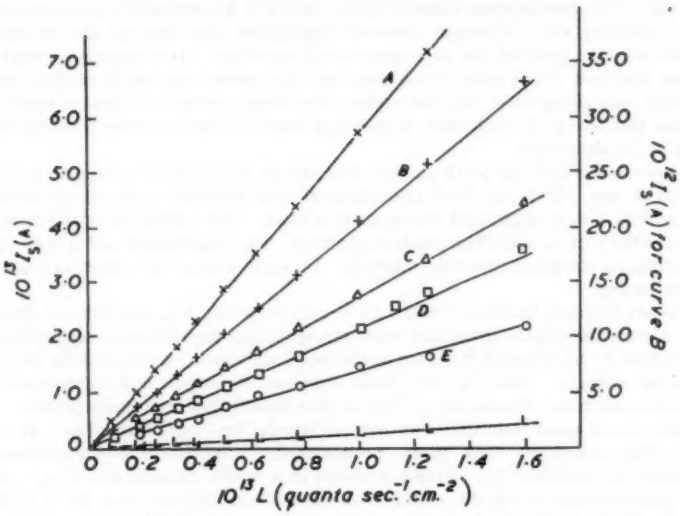
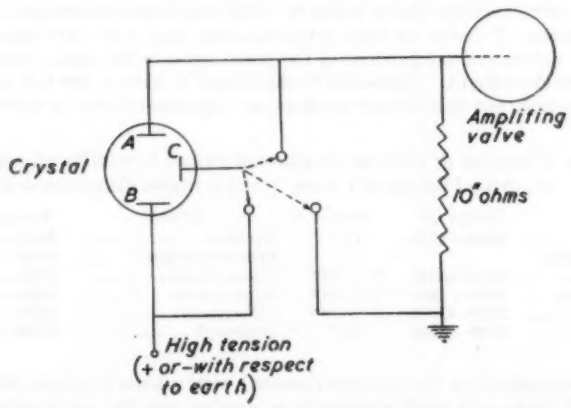
FIG. 4. *Surface current–light intensity curves.*



Crystal	Crystal size	Field (v cm.$^{-1}$)
A Chrysene	3 mm. × 1 mm.	2300
B Anthracene	2 mm. × 2 mm.	500
C Pyrene	4 mm. × 1 mm.	4000
D 1 : 2-5 : 6-Dibenzanthracene ...	2 mm. × 1 mm.	500
E Pyrene	4 mm. × 1 mm.	2000
F Chrysene	3 mm. × 1 mm.	400

FIG. 5. *Schematic diagram of bulk-current experiments.*



A and *B* are electrodes on one face (001) of a thin (10 μ) anthracene crystal, *C* is an Aquadag ring on the opposite face (001) of the crystal, but of such a diameter that *A* and *B* are within it. Direct connection was made between *C* and *A*, *B*, or earth. The light shines wholly within the ring.

10^{13} quanta sec.$^{-1}$ cm.$^{-2}$ over a 200-fold range of applied voltage. For a comparable voltage and light intensity, I_B was estimated as about 1—10% of I_S.

The effect of variation of the area of illumination was studied for the surface cell. Before any experiment was begun the whole crystal was irradiated to render it free from space charges. After our irradiating the whole area between the electrodes, then switching off both the light and the field, and then reirradiating it, I_b was very small, about 1/50th of the original forward current. However, by using a light probe at various positions between the electrodes both an I_p and an I_b were obtained. The maximum current I_p was approximately constant for different positions of the probe between the electrodes. A similar result was obtained if the two electrodes were on one (001) face of the crystal, well away from the edges, and a probe was moved across the opposite (001) face. When the probe moved beyond an electrode I_p decreased rapidly as did the steady current I_c. When the probe light fell on the face of the crystal which held the electrodes (the field being on throughout), switching the light off and then on again after only a short interval restored I to the steady value, I_c, less than I_p. If, however, the probe was moved before switching the light on again I reached a peak.

TABLE 2. *Photocurrents in anthracene single crystals.*

Primary light (in applied field)	Secondary light (probe) (no applied field)	Current observed with secondary light (f, forward; b, back)
(1) Overall	Near either electrode	I_b, small
(2) ,,	Central area	I_b, smaller than in (1)
(3) Probe near either electrode	Central area	I_f
(4) ,, ,,	Same area as primary	I_b, large
(5) ,, ,,	Near other electrode	I_b, smaller than in (4)
(6) Probe in central area	Central area	I_b, large
(7) ,, ,,	Near either electrode	I_f, small

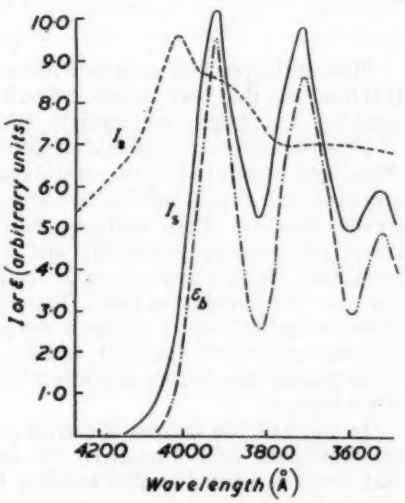


FIG. 6. *Spectral dependence of I_B and I_S for anthracene compared with crystal absorption spectrum.*

b-Polarisation; see Bree and Lyons, *J.*, 1956, 2662.

The current scale is different for each curve; readings at all wavelengths are relative to that of the first peak. The number of incident quanta is the same for all wavelengths.

I_B, crystal 10 mm. × 10 mm. × 5 mm.; applied voltage 500 v.

I_S, crystal 5 mm. × 2 mm. × 2 μ; field 1000 v cm.$^{-1}$ with uniform illumination.

Other experiments where two electrodes were used are listed in Table 2. These show the conditions for obtaining a back current I_b, and also for obtaining a forward photocurrent, I_f, even in the absence of an applied field.

Experiments were performed with three electrodes of which two, *A* and *B*, were on one (001) face of an anthracene crystal and the third, *C*, a ring of about 4 mm. internal diameter, on the opposite (001) face. The light was incident on the ring side and fell only within the ring. Connections were made as in Fig. 5. The results are shown in Table 3. A current is indicated as negative when electrons flowed from earth to the grid of the valve. A large current was obtained only in the cases (iv) and (v) when *C* was at a potential considerably different from that of *A*. Consequently the experiments showed that current passes through the bulk of the

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crystal and does not flow only along the surface. Since the current in (iv) was much larger than that in (v) there is additional evidence that the carriers are positive holes. Experiments

TABLE 3. *Photocurrents with three electrodes, A, B, and C.*

	(i)	(ii)	(iii)	(iv)	(v)
Potential of *B* (v)	450	−450	+450	220	−220
Potential of C (v)	0	0	floating	220	−220
I (arbitrary units)	−10	−7	+60	+8000	−300

with a guard ring were made with sandwich cells; it was shown again that a current actually passed through the bulk of the crystal and did not need to pass along the surface.

Current–Wavelength Relation.—With the surface cell, the spectral dependence of I_S is described in general by a curve which resembles the absorption spectrum, varying with the polarization of the light in a way which is semiquantitatively similar. These results will be discussed fully in a later paper.

With the sandwich cell the close similarity of the spectral-dependence curve to the absorption spectrum was lost (see Fig. 6). The chief features observed with the sandwich cell are the loss of structure in the spectral dependence curve (only one maximum was obtained, somewhat displaced towards the red from the first maximum found with the surface cell), and the presence of an appreciable current at wavelengths towards the red end of the absorption system.

DISCUSSION

Most of the previous work on anthracene has been concerned with the surface currents. It is now clear that both surface and bulk currents occur and the dependence of the current upon, *e.g.*, wavelength, field strength, and surrounding gas is different in the two cases.

Processes occurring.—An overall picture of the processes thought to occur is as follows. When light is absorbed by the crystal some is re-emitted as fluorescence, some is thermally degraded, and a small fraction liberates current carriers, of which positive holes have the greater mobility. Both electrons and holes may be trapped. A rise in temperature lowers the trapping probability and so the photocurrent has a positive temperature coefficient. Space charges occur at the electrodes and, if the light falls on a limited area, also over this illuminated area. These are due to trapped carriers. Also, in the surface layers, a double layer of charge is assumed in order to explain the properties of surface currents such as carrier mobility, which is greater in the surface than in the bulk. Variation in the gaseous atmosphere may affect both the double layer and the production of carriers at the surface.

In the bulk the current is carried predominantly by positive holes [22,21,4] even when monochromatic light of relatively low wavelength (2240 Å) is used. It may be supposed that electrons have a smaller mobility than the holes in order to explain that $I_+ > I^-$ (where I_+ and I_- are the currents carried by positive holes and electrons respectively). The reason for this may well be that the positive electron affinity of anthracene molecules [23] results in a high probability of trapping at each molecular site. In addition, it is possible that an absorbed gas such as oxygen may act as an electron trap. The ion O_2^- is known to exist both in the free state and in crystals, but there is no evidence yet as to just how the electron is held on the crystal surface. In the surface cell also $I_+ > I_-$, but the values are much more similar than those in the bulk, indicating that the electrons carry a greater fraction of I_S than of I_B.

When light is absorbed, migration of energy is known to occur [24] and any quantum will make about 10^5 hops to neighbouring centres before fluorescence occurs. The probability of a transition to an ionized state must be very much less than the probability of fluorescence, in view of the fact that the occurrence of photoconduction leaves the fluorescence yield (about 0·9) unchanged. A low probability of ionization is consistent with the estimated

[22] Putseiko, *Dodlady Akad. Nauk S.S.S.R.*, 1949, **67**, 1009.
[23] Lyons, *Nature*, 1950, **163**, 193.
[24] Bowen, Mikiewicz, and Smith, *Proc. Phys. Soc.*, 1949, *A*, **62**, 26; Simpson, *Proc. Roy. Soc.*, 1957, *A*, **238**, 402; Dexter, *J. Chem. Phys.*, 1953, **21**, 836; Ferguson, *Austral. J. Chem.*, 1956, **9**, 172.

quantum efficiency of carrier liberation. Although carrier liberation scarcely affects fluorescence, it is possible that it is comparable in efficiency with the thermal degradation of the absorbed energy. Recombination of positive holes with electrons, possibly with the occurrence of fluorescence, is also expected to occur. Consequently, not all the carriers liberated will reach the outer circuit.

Surface Current.—For I_S, many of the results are summarized for a given electrode separation and for uniform illumination by monochromatic light, by the relation

$$I_S \propto \varepsilon[O_2]_{ads.} . vL^n \exp(-2300/T) . f(t) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where ε is the extinction coefficient, $[O_2]_{ads.}$ the surface concentration of adsorbed oxygen, v the applied voltage, L the total light intensity incident on the crystal, n a number between 0·5 and 1·0 (often 1·0), T the absolute temperature, and $f(t)$ a function of the time of illumination. The dependence of I_S upon ε, $[O_2]_{ads.}$, and T is discussed elsewhere.[7,25] The relation (1) is to be regarded as approximately correct over a wide range of the variables. Some deviations will be mentioned below.

The actual process by which carriers are produced appears to be limited to three possibilities. The excited crystal level may undergo a transition directly to an ionized state or else ionization may be induced by the presence of an electric field [26] or of a molecule such as O_2. There are various fields present in the crystal, as well as the applied field which has been suggested [10] as responsible, namely (*a*) the local field surrounding an ion already produced, which at the nearest-neighbour distance is expected to be of the order of 10^7 v cm.$^{-1}$ and to fall off to about 200 v cm.$^{-1}$ at about 1000 Å distance; (*b*) the field near the surface which may act as a part of a diffuse double layer [27,6] [this is related to (*a*) since charges may be trapped in the surface layer]; and (*c*) space-charge fields already mentioned, also built-up from fields of type (*a*). Any field present would of course have some effect. The various transition probabilities are not known. For light absorbed near a surface, (*b*) is likely to be important and may play a part in explaining the spectral dependence of I_S, along somewhat similar lines to those previously suggested.[28] However, for ionization in the interior of the crystal (*b*) will not be relevant. Since I_S is decreased by removal of the oxygen in the surrounding atmosphere it was previously postulated [7] that some oxygen–anthracene compound was an intermediate in the production of current carriers. Nitric oxide, sulphur dioxide, and other gases behave similarly to oxygen,[6,7] but whilst compounds are definitely formed [7] with oxygen, nitric oxide, and sulphur dioxide, it is possible that these have nothing to do with carrier liberation. The effect of gases on the photocurrent now seems more likely [6] to be by way of a double-layer effect either on the efficiency of carrier production or on the mobility of carriers when formed or else on both the production and the mobility.

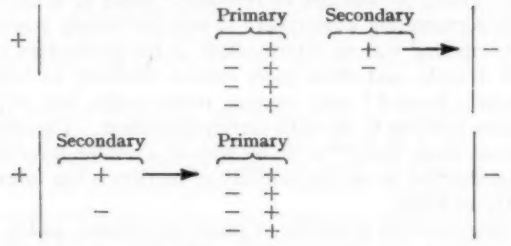
Double layers of charges occur generally at phase boundaries, and so may be expected at the crystal–gas (or crystal–vacuum) interface. The idea of a double layer can be used to interpret the result shown in Fig. 2. The build-up time of I_S was decreased by prior illumination in the absence of a field. On the assumption that light by itself does not give rise to space-charge effects at the electrodes, it is possible to conclude that in air the light liberates charges in the surface layers and these then alter the charge distribution in the double layer. Eventually, if the double-layer distribution becomes nearly constant, then I_S should become steady, as is observed.

Space charges near the electrodes, even if not produced by uniform illumination of the crystal, are certainly present whenever a field is present, and decay when the field is switched off. Evidence for electrode space charges is seen in the fact that reversal of the applied voltage caused a temporary diminution in I_S, which gradually returned to its

[25] Bree and Lyons, unpublished work.
[26] Zener, *Proc. Roy. Soc.*, 1934, **145**, *A*, 523.
[27] Bardeen, *Phys. Rev.*, 1947, **71**, 717.
[28] Lyons, *J. Chem. Phys.*, 1955, **23**, 220.

original value. The use of alternating fields is essential to eliminate such effects. Electrode space charges account for the result of experiment (5) in Table 2. The electrode space-charge field is smaller than the field due to space charges produced by a light probe in a neighbouring area; this is seen from experiment (7) in Table 2, because the secondary light produced a forward and not a back current. Non-uniform illumination [experiments (4), (5), and (6) of Table 2] shows clearly how the light produces a space-charge field which is predominantly situated in the area of the light beam and largely remains during the interval before the secondary illumination. This we explain by the trapping of the electrons near the place of their formation whilst the positive holes move in the field a certain distance (small in comparison with the size of the light spot) but cannot easily escape from the region of negative charge. When trapped, the holes set up with the electrons a reverse space-charge field and further movement of holes is randomly directed. Trapped electrons constitute a likely trap for positive holes. Different trap-depths would be given by different distances of separation of the positive and negative centres. Recombination of holes with electrons takes place in the dark but is assisted by re-illumination (secondary light). In this way experiment (6) of Table 2 is explained. It does not follow that the secondary light produces recombination of only those holes and electrons formed by the primary. More charges will be produced by the secondary light and the electrons freed by the primary light may combine with secondary holes and *vice versa*. On this view, I_b is not caused by the " de-trapping " of electrons and holes. In the secondary light all wavelengths were equally effective, and evidence of different trap depths was found in such experiments. From experiments (7) and (3) it is seen that the charge separation produced by the primary light may be neutralized as a result of the secondary light on a different area, the charges flowing in the forward sense, indicated in positive holes by the arrows in Fig. 7. For experiments (1) and (2) the small value of I_b shows that a small space-charge field is situated near the electrodes.

FIG. 7. *Schematic diagram showing how I_t and I_b arise from secondary illumination because of space-charge fields due to the primary light* (*cf. Table* 2).



An ingenious experiment by Goldsmith [4] may be interpreted on a similar basis. He applied simultaneously a uniform background illumination of variable intensity over all the crystal and a probe light-spot of constant intensity. The currents due to the probe were found to increase to a maximum with increasing intensity of background light. It was concluded that the background light liberated carriers from a certain class of trap. We now suggest that the function of the background was to produce charges over the entire area of the crystal so that no space-charge field could be built up by the probe light. From the experiment it is seen that the probe space charge became negligible when the background light produced a current about four times as great as that due to the probe light. In other words, the carriers produced by the background light were sufficiently numerous to neutralize any charges from the probe which otherwise would have given rise to a space-charge field. This explanation does not contradict Goldsmith's, but is rather an amplification of it.

Current–Field Relation.—Surface current–field strength curves are nearly linear and this justifies the use of a relation such as $I_S = p\mu_S F$, where p is the number of carriers, μ_S their average mobility in the surface layers, F the field, assumed nearly equal to the applied voltage/cm. Deviations from linearity may be due to the presence of space charges at the electrodes, which are not proportional to V. Evidence for this is that I_b (relative to the forward current) is larger at lower values of V. They may also be due to the variation of the field in a direction, ϵ, perpendicular to the surface. Both p and μ_S are expected to depend on z. Consequently the accurate expression for I_S will be complicated and deviations from linearity between I_S and V therefore expected. A further cause of deviation may be the necessity of a field for the production of some of the current carriers. However, this has not been established. Bad electrode contacts gave deviations from linearity in the opposite sense to that shown in Fig. 3(*a*).

The values of p and μ_S must be derived from conduction measurements since no Hall-effect measurements have been reported for hydrocarbons. Since I_S was proportional to L, in the range considered, the relation $I_S = p\mu_S F$ is further substantiated provided that $p \propto L$. This is true even when p is taken to include both electrons and positive holes. It may be inferred, furthermore, that the recombination of carriers follows first-order kinetics. Since the decay of I_S when the light is switched off is of first-order, this decay process may be attributed to recombination of carriers.

The mobility can be estimated in several ways. Some values obtained previously and also some new ones are shown in Table 4. If b is disregarded because it applies to a film and not to a single crystal, and the other values are assumed to be comparable, then $5 \times 10^{-3} < \mu < 10^3$ cm.^{2} v^{-1} sec.$^{-1}$. However, since a, c, and d presumably refer to μ_B

TABLE 4. *Mobilities (cm.^{2} v^{-1} sec.$^{-1}$) in anthracene.*

No.	Value	Ref.	Method
a	10^{-2}	11, 29	Semiconduction of single crystals, the number of molecules able to yield carriers being assumed to be 10^{21} cm.$^{-3}$.
b	$10^{-4 \cdot 1}$	10	As for *a*, but with use of other values for the activation energy (0·96 ev) and conductivity of films.
c	1·0	21	Mean free path, λ_e (estimated as 10^{-4} cm. from the saturation of I_B with F when the negative electrode of a sandwich cell was illuminated), and the carrier life-time τ (estimated as 5×10^{-8} sec. by comparison with life-times obtained in certain inorganic crystals having a high trap density) through $\lambda_e = \mu\tau F$.
d	5×10^{-3}	4	As *c*, with an experimental value for τ.
e	10^2	4	From the range of the carriers (calc. as 0·1 cm. from the field distribution on a crystal surface determined by light-probe expts.) and τ (taken as 10^{-5} sec.) through Range $= \mu\tau F$ (cf. *c* and *d*) .
	$10^{-2}/Q$	—	Q is the ratio of carriers produced to quanta absorbed; it is likely to be less than unity for any hydrocarbon and $<0{\cdot}1$ for anthracene which has a high fluorescence yield. [μ was taken as $I_B/(LQ\tau F)$; $I_B/(LF)$ is given in Table 1 and τ was taken as 10^{-5} sec.] This gives the value $\mu = 10^{-2}/0{\cdot}1 = 10^{-1}$.
g	*ca.* 10^3	—	By assuming that the drift mobility is related to the thermal velocity u (10^7 cm. sec.$^{-1}$) of an electron by $\mu = u \exp(-E_T/kT)$, where E_T is the depth of the trap below the conduction band, and was assumed to be measured by the temperature coefficient of I_S which is [25] 0·2 ev.

for the crystal bulk and *e*, *f*, and *g* to μ_S, for the surface layers, it may tentatively be concluded that $10^{-3} < \mu_B < 1$ and $10^{-1} < \mu_S < ca.\ 10^3$.

Photo-experiments on the bulk crystal usually give space-charge effects which lower the value of I_B and therefore restrict us to semiconduction measurements to obtain μ_B. The value of μ_B, 10^{-2}, for single crystals [29] (in the 001 plane) assumes that anthracene is an intrinsic semiconductor, a conclusion which is compatible with the correlation of the activation energy of conduction with a molecular property.[31, 10]

[29] Mette and Pick, *Z. Physik*, 1953, **134**, 566.
[30] Shockley, "Electrons and Holes in Semiconductors" (van Nostrand, N.Y., 1950), p. 240.
[31] Carswell, Ferguson, and Lyons, *Nature*, 1954, **173**, 736.

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If μ_S is taken as 10^3 and since $\tau = 10^{-5}$, $L = 10^{13}$ and $Q = I_S/(\mu L \tau F)$, then $Q = 10^{-5}$. The assumption that $Q < 10^{-1}$ (as seems probable) leads to a value of μ_S greater than 10^{-1} which is again consistent with μ_S being greater than μ_B.

Bulk Current.—I_B is smaller than I_S owing both to the space charge and lower mobility in the bulk. The existence of space charge accounts for the I_B–t curve which shows the typical drop from a peak to a steady value.

Current–Voltage Curves.—I_B–V curves [Fig. 3(*b*)] are markedly non-linear. This is explained by the build-up of space charge. No current saturation was obtained upon increasing the voltage when the light fell on the negative electrode, although the current increased only slightly. The I_B–V curve differed according to the electrode illuminated. This difference is the basis of determining the sign of the carriers.

Current–Light Intensity Curves.—I_B–L^n curves gave n different from unity (about 0·5) only in the case when the negative electrode was illuminated. This was due to either a bimolecular process of carrier removal or else a distribution of traps above the Fermi limit of the type described elsewhere.[32] The charge distribution in the crystal should depend on which electrode was illuminated since the mobilities of electrons and positive holes are different. Different distributions of charges are assumed to give rise to different kinetics of carrier removal.

Spectral Dependence.—The difference in the spectral dependence of I_B and I_S may be associated with the greater distance of penetration of the light at wavelengths above 4100 Å. The greater the penetration the less will the carriers produced be affected by the surface layers. In accordance with this view, I_B is altered much less than I_S by the surrounding atmosphere. The existence of a current above 4100 Å indicates a small positive extinction coefficient of the crystal. Such small values of ε have not yet been measured. At low temperatures the Boltzmann bands of the absorption spectrum disappear and consequently the long-wavelength tail of the spectral-dependence curve should also disappear. This experiment would therefore provide a test of the explanation just given.

The substances other than anthracene which were examined differed only in the magnitudes of the currents obtained. Both the production and the mobility of carriers are likely to be different in each case. The order of arrangement of the compounds in Table 1 is closely similar to the order of arrangement by a number of molecular properties, *viz.*, the energies of transition to the first excited singlet and triplet levels, the molecular-ionization energy, the molecular electron affinity, the maximum free valency in the molecule, the minimum atom localization energy and the radical affinity. The ease of aerial oxidation of the molecules may also be correlated. Which of the molecular properties is most significant will be considered elsewhere.

Department of Physical Chemistry,
University of Sydney, Australia.

[*Received, December 28th,* 1956.]

[32] Rose, *R.C.A. Revs.*, 1951, **12**, 362.

723. *Photo- and Semi-conductance in Organic Crystals. Part IV.* Spectral Dependence of Photocurrents in Aromatic Hydrocarbon Crystals in Dry Air with Polarized Light.*

By L. E. Lyons and G. C. Morris.

A surface current, I_S, may arise whenever light falls in an electronic absorption region of a crystal of an aromatic hydrocarbon. The polarization of the light affects I_S in a way similar to its effect on the extinction coefficient. Consequently conclusions can be drawn about electronic transitions in the crystal from measurements of I_S. Observed polarizations are given for anthracene, chrysene, pyrene, and 1 : 2-5 : 6-dibenzanthracene, and their significance for the theory of electronic excited states is discussed.

The spectral dependance of the bulk current, I_B, differs from that of I_S. This is attributed to the fact that carriers liberated in the bulk are independent of a surface effect such as that which explains the curve of surface current against frequency.

The surface photocurrent, I_S, in anthracene and tetracene crystals [1-4] depends on the plane of polarization and upon the wavelength of the incident light in a way which makes the curve of surface current against frequency, ν, resemble the absorption spectrum of the crystal. This knowledge is now extended to the second main absorption system in anthracene and several other hydrocarbon crystals in polarized light, for which we had previously reported results only with unpolarized light.[5]

Experimental and Results

Crystals were prepared and purified as previously.[6] Crystal structures and optical data [7] are known, naphthalene,[8] anthracene,[9] phenanthrene,[10] chrysene,[11] and pyrene [12] being monoclinic, and 1 : 2-5 : 6-dibenzanthracene [13] being either monoclinic or orthorhombic. For the monoclinic crystals, the *ab* plane was the well-developed cleavage face, but the *ac* plane was developed for dibenzanthracene. For surface currents, a sublimation flake was placed on a silica disc and extinction directions found and distinguished (under a Zeiss polarising microscope) conoscopically. For electrodes, " Alkadag " was painted parallel to a crystal optical direction. For bulk currents, the experimental arrangement was as before.[6] Light sources were a fan-cooled 1000 w projection lamp, a 12v/60 w tungsten filament, a high-pressure mercury lamp in quartz, and a " Vitreosil " hydrogen discharge. Light, dispersed by a Beckman monochromator, was polarized by a Wollaston prism unit. Two rectangular images (*ca.* 2 mm. × 10 mm. and separated by 2 mm.) of the exit slit were each plane-polarized mutually perpendicular. Careful alignment was necessary to ensure that the beams were symmetrically disposed so that, with one always masked, vertically and then horizontally polarized light could be placed on the crystal by rotation of the prism. The lamps were calibrated with a Schwarz linear thermopile of sensitivity 2·2 μv/μw at the exit slit for unpolarized and, in place of the crystal, for polarized light. The projector and mercury lamp were calibrated directly, then the latter used to calibrate a 1P28 photomultiplier which was then

* Part III, preceding paper.

[1] Part II, Carswell and Lyons, *J.*, 1955, 1734.
[2] Lyons, *J. Chem. Phys.*, 1955, **23**, 220.
[3] Carswell, Ferguson, and Lyons, *Nature*, 1954, **173**, 736.
[4] Bree and Lyons, *J. Chem. Phys.*, 1954, **22**, 1630.
[5] Lyons and Morris, *Proc. Phys. Soc.*, 1956, **69**, 1162.
[6] *Idem*, preceding paper.
[7] Sundarajan, *Z. Krist.*, 1936, **93**, 238; Winchell, " Optical Properties of Organic Compounds," Univ. of Wisconsin Press, 1st Edn., 1943; Krishnan and Banerjee, *Z. Krist.*, 1936, **91**, 170.
[8] Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 233.
[9] Mathieson, Robertson, and Sinclair, *Acta Cryst.*, 1950, **3**, 245.
[10] Basak, *Indian J. Phys.*, 1950, **24**, 309.
[11] Iball, *Proc. Roy. Soc.*, 1934, *A*, **146**, 140.
[12] Robertson and White, *J.*, 1947, 358.
[13] *Idem, ibid.*, p. 1001.

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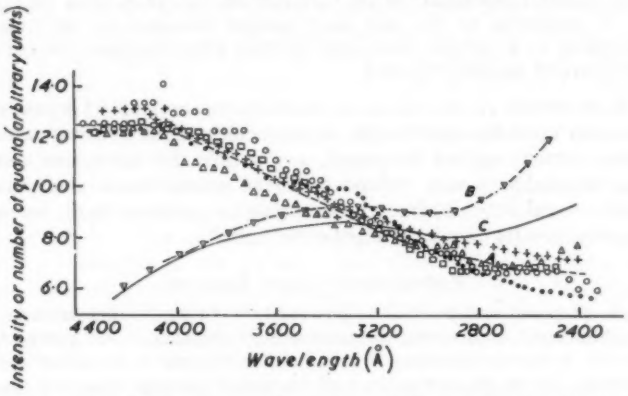
used to calibrate the hydrogen lamp. Variations in slit widths were avoided by the use of nickel gauze filters and lens diaphragms. Two different mercury lamps were each used with three photomultipliers, their spectral response curves being similar to those listed by the manufacturers. Fig. 1 shows the calibration curve for the hydrogen lamp. Thus, for this lamp we have (*a*) the number of photons and (*b*) energy distribution (in ergs) with fixed monochromator slits, (*c*) number of photons at exit slit with constant wave-number bandpass ($\Delta\nu$), (*d*) quantal distribution with variable entrance and exit slits and constant $\Delta\nu$. Stray light can cause spurious effects such as long-wavelength tails in the photocurve. Filters were used to check the presence of this stray light, and ensure that its intensity was insignificant. At lower wavelengths (*ca.* 2200 Å), its level reached undesirable proportions but no determinations of photocurrent were made below 2500 Å as photoelectric emission from the electrode assembly became noticeable. The ratio I_x/I_y of the currents obtained with the light polarized in the

FIG. 1. *Intensity output of Vitreosil hydrogen lamp.*



A. At exit slit of Beckman monochromator with fixed entrance and exit slits.

△ Photomultiplier No. 1 calibrated by mercury lamp 1.
\+ Photomultiplier No. 1 calibrated by mercury lamp 2.
○ Photomultiplier No. 2 calibrated by mercury lamp 1.
□ Photomultiplier No. 2 calibrated by mercury lamp 2.
● Photomultiplier No. 3 calibrated by mercury lamp 1.

B. Relative number of quanta emitted by Vitreosil hydrogen lamp at each wavelength setting used in determination of polarized photocurves.

Full line calculated from *A*.
▽ Experimentally determined.

C. Curve *B* corrected for absorption by Wollaston unit.

directions *x* and *y* was obtained at any particular wavelength by taking successive current readings with horizontally and then vertically polarized light on the crystal. A standard (1 min.) build-up and decay time was chosen with repetition of current readings until constancy of the ratio ($\pm 0{\cdot}02$) was obtained. For photocurves the method was similar, readings also being repeated of peaks and minima in case the current values had increased with time.[6] The method of, and reasons for, altering slit widths at each wavelength has been discussed.[1] The correction for variation in lamp emission obtained from (*d*) (see Fig. 1) was the only correction necessary.

Ratios I_b/I_a.

Wavelength (Å)	3131	3021	2964	2803	2643	2560
Frequency (cm.$^{-1}$)	31,939	33,102	33,738	35,676	37,836	39,063
Naphthalene	1·3	1·2	1·1	1·3	1·1	1·1
Phenanthrene	1·1	—	—	—	—	—

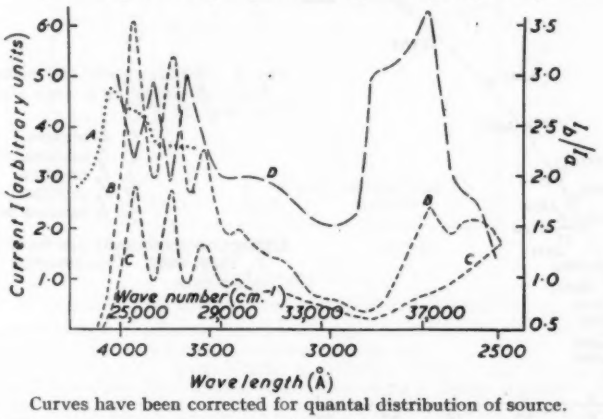
The results of the experiments are shown in Figs. 1—6 and the Table. For most substances the crystal spectrum is not available and there is shown in the diagrams a spectrum based on the

solution spectrum but with approximate estimated corrections to allow for the shift of wavelength of absorption with change of phase. These corrections are based upon the shifts observed in going from the spectrum of the solution to the I_S–ν curve of the crystal.

The magnitude of the current was often so small that a very wide slit was used. Consequently the resolution is not as good as could be desired and therefore, for example, the value of I_b/I_a is less than would be obtained otherwise. Lack of resolution should not affect the relative change of I_b/I_a with ν. In interpreting the plots of I_b/I_a against ν the emphasis should be on the way in which the ratio changes rather than upon its absolute value. As well as the effect of a wide slit in lowering I_b/I_a, there is another effect which is especially pronounced in substances like naphthalene, where the current is very small. The presence of a bulk current comparable in magnitude with I_S is more likely with, say, naphthalene than with anthracene. As a result it is more difficult to draw conclusions about the absorption spectrum from currents in naphthalene than from those in anthracene.

The alteration of the polarization ratio due to a misalignment of 1° or 2° of the electrodes was calculated as negligible. No dependence of I_b/I_a on field direction or on light intensity was found, but with non-uniform illumination of the crystal I_b/I_a changed slightly with voltage.

FIG. 2. *Spectral dependence of the photocurrent from single crystals of anthracene.*



Curves have been corrected for quantal distribution of source.

A. Bulk current. Crystal 5 mm. thick. Field parallel to *c'*-axis. Voltage applied = 500 v.
B. Surface current when light is polarized along the *b*-axis of the crystal.
C. Surface current when light is polarized along *a*-axis of crystal.
For *B* and *C*, crystal is 2 μ thick, and field direction is along *b*-axis. Field = 1000 v/cm.
D. Current ratio I_b/I_a.
Current scale is same for *B* and *C*, but differs for *A*. Spectral bandpass 750 cm.$^{-1}$.

DISCUSSION

Results with both unpolarized and polarized light show that I_S arises whenever radiation falls within an absorption region of the crystal. The earlier conclusion [3] to this effect is accordingly substantiated.

Anthracene.—The spectral dependence has been discussed before [1,2] and a close relation between I_S and ε (extinction coefficient) observed in the first absorption region. In the second region, with unpolarized light the linear relation of I_S and ε did not hold well, as was to be expected; however, for ν >37,000 cm.$^{-1}$, I_S–ν and ε–ν curves were entirely different. This was puzzling but the great experimental difficulties in that region were thought to be responsible. More recently the crystal spectrum has been determined with polarized light.[14] Fig. 2 shows a determination of the I_S–ν curve recorded with polarized light for a constant number of incident quanta at each wavelength. Corrections have been applied to allow for the quantal distribution of the source and absorption by the

[14] Bree and Lyons, *J.*, 1956, 2662; Craig and Hobbins, *J.*, 1955, 539.

optics (see Fig. 1). It is now clear that a resemblance between the I_S–ν and the ε–ν curves exists even in this second absorption region. At still higher energies the resemblance should decrease because of photoelectric emission from the surface of the crystal. A plot of ε against ν is shown in Fig. 3. For the lower values of ε the relation is approximately linear and thus supports the earlier theory,[2] *i.e.*, the excitation energy regains the surface and then liberates carriers. The further into the crystal the photon penetrates the less chance does it have of regaining the surface. It is not necessary [6] to assume that the liberation of carriers is greater at the surface than in the bulk; this may still be true, but a varying mobility of carriers between bulk and surface must also be considered. In any event, the main point of the theory is preserved—the excitation or the carrier regains the surface. The surface effect is expected to be less important for a large single crystal in a sandwich cell and the resemblance to the absorption spectrum therefore should be lost. Fig. 2, *A* shows the spectral dependence of the bulk photocurrent for a crystal several

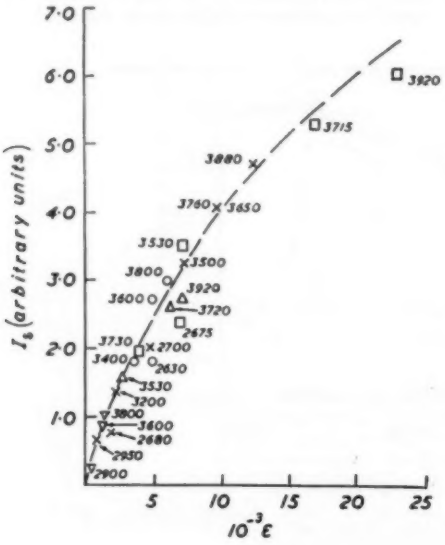


FIG. 3. *Surface current (I_S) plotted against extinction coefficient (ε) for a single crystal of anthracene (cf. Fig. 2).*

□ I_b maxima.
○ I_b minima.
△ I_a maxima.
▽ I_a minima.
× I_b random points.

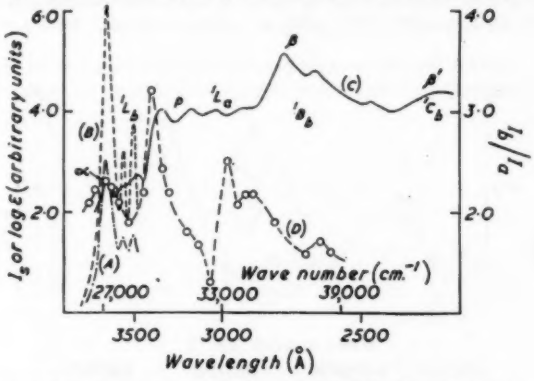
Extinction coefficients are from Bree and Lyons, *J.*, 1956, 2662. Wavelengths (Å) are stated beside points.

millimetres thick. For measurable values of I_B a tungsten source was necessary, so only part of the first transition is observed. This curve differs markedly from that for the surface current I_S, and to a certain extent, therefore, the "surface theory" for I_S–ν curves is confirmed. Further points in favour of the theory are: (i) I_B is much less affected by changes in the surrounding atmosphere than is I_S; [6] (ii) the ratio of I_b/I_a for the above crystal is unity at 4000 Å and in the absorption region. A current up to wavelengths of about 4400 Å for a crystal 5 mm. thick is explicable without additional assumptions if the absorption is regarded as taking place from a ground level which contains vibrationally excited molecules. For a thick crystal which absorbs all light incident at any wavelength the current is expected (all surface effects being neglected) to be independent of ν. The existence of a peak in the I_B–ν curve appears therefore to be due in some way to the double layer which is known to exist at the electrode.[6]

Chrysene.—At wave numbers 26,000—29,000 *cm.*$^{-1}$. Fig. 4 shows clearly that there is a general resemblance to the absorption spectrum in this region. The wavelength shift from the solution spectrum in 95% ethanol to the crystal I_S–ν curve is 420 cm.$^{-1}$ for the first transition and rather greater, *ca.* 1350 cm.$^{-1}$, for the component of the second transition observed near 30,000 cm.$^{-1}$ in the crystal. If the resemblance between I_S and ε curves be

accepted then it is clear that in the first transition absorption is stronger in the *b* crystal direction than in the *a*. On Platt's theory [15] this transition should be long-axis polarized. The band is analogous to the 31,642—31,476 cm.$^{-1}$ system in a naphthalene crystal and a similar explanation should exist for both naphthalene and chrysene long-wavelength systems. If therefore the naphthalene upper state is assigned as B_{3u} (in D_{2h}), ^1L_b, then the chrysene is also ^1L_b—long-axis polarized. Strictly speaking, the chrysene molecule is of a lower symmetry than naphthalene, being C_{2h} instead of D_{2h}. Consequently the *x* (longer) and *y* (shorter) in-plane directions both belong to the same irreducible B_u representation of the symmetry group. The effect of this on the spectrum should be to mix the B_{2u} and B_{3u} upper states. Hence in chrysene the intensity of the ^1L_b transition should be rather more than in, say, naphthalene. This is actually the case. For chrysene $f = 0{\cdot}005$; for naphthalene $f = 0{\cdot}002$; however the different size of the molecules is another factor

FIG. 4. *Spectral dependence of the photocurrent from single crystals of chrysene.*



Curves have been corrected for quantal distribution of source.

A. Surface current when light is polarized along the *a*-axis of crystal.
B. Surface current when light is polarized along *b*-axis of crystal.
C. Absorption spectra of solutions (from Friedel and Orchin, "Ultraviolet spectra of aromatic compounds," Wiley, New York, 1951) shifted to allow for effect of change of phase. For 1st transition shift is 420 cm.$^{-1}$, for 2nd transition 1350 cm.$^{-1}$. The 3rd and 4th systems are likewise moved 1350 cm.$^{-1}$ although the actual shift might be expected to be greater.
D. Current ratio I_b/I_a. Spectral bandpass for (*A*), (*B*) and (*D*) is *ca.* 750 cm.$^{-1}$.
Crystal thickness 2·5 μ. Field direction along *b* axis. Field 750 v/cm.

which has to be considered. The ^1L_b transition has not been measured in absorption in tetracene and anthracene which are closer in size to chrysene than is naphthalene.

The only justification for speaking of "long-" and "short-axis" transitions in chrysene molecules is that the analogy with the linear polyacenes is preserved, *e.g.*, in the crystal structure and in the solution spectra. A long-axis transition in chrysene on the oriented-gas model will probably give rise to a greater absorption in the *a* crystal direction than in the *b*. (A comparison of the unit-cell dimensions of naphthalene, anthracene, and chrysene shows that the long axis of the chrysene molecules lies nearest to the *c* crystal direction, a situation which results, for both naphthalene and anthracene, in a greater component along *a* than along *b*. If it happens that the reverse is true with chrysene, the observed I_b/I_a ratio is directly explicable.) The explanation of I_b/I_a being greater than unity when the transition is long-axis polarized may be given in terms of intensity stolen from the *a* component of the next (stronger) transition and added to the weaker component of this transition, thus reversing the expected polarization ratio. Such is the theory given [16] for the long-wavelength naphthalene system and a similar situation must be presumed in

[15] Platt, *J. Chem. Phys.*, 1949, **17**, 484.
[16] McClure, *ibid.*, 1954, **22**, 1668.

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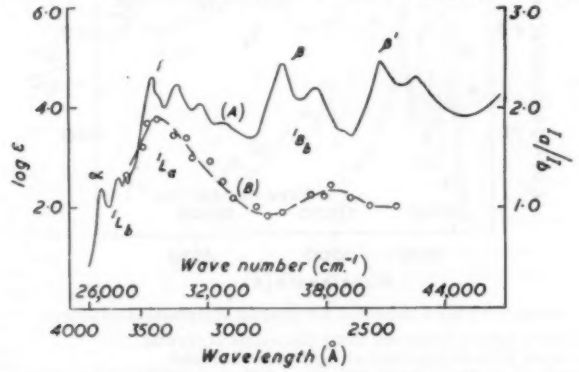
chrysene. Intensity stealing by a crystal mechanism has been measured [14] in anthracene. The transition can therefore be assigned to a ^1L_a upper state even though the I_b/I_a ratio is greater than unity.

At wave numbers 29,000—33,000 *cm.*$^{-1}$. This region corresponds to the second main absorption system, Clar's " *p* " band,[17] assigned by Platt to a ^1A–^1L_a transition, short-axis polarized, analogous to the transition to a B_{2u} upper state in naphthalene, anthracene, and tetracene. In the naphthalene A_g–B_{2u} transition, the splitting was calculated [18] as 100 cm.$^{-1}$ by a method which used the known intensity of the transition instead of an explicit form for the one-electron wave functions. The other method may have given a larger answer as the result [19] obtained for an A_g–B_{1u} transition ($f = 0{\cdot}1$) in benzene, explicit wave functions being used, was 540 cm.$^{-1}$. If it is correct with chrysene to identify the low I_b/I_a value at 32,600 cm.$^{-1}$ as due to the presence of an *a* component of the second transition, then the splitting between the *b* and *a* components is over 540 cm.$^{-1}$. This high value may be due to what differences exist in the somewhat similar crystals structures of chrysene ($I2/c$) and naphthalene ($P2_1/a$). There should be in chrysene four split

FIG. 5. *Spectral dependence of the photocurrent from single crystals of pyrene.*



A. Absorption spectra of solutions (from same source and shifted as for Fig. 4, *C*).
B. Current ratio I_b/I_a. Spectral bandpass is *ca.* 750 cm.$^{-1}$. Crystal thickness *ca.* 3·0 μ. Field direction along *a* axis. Field 600 v/cm.

components compared with the two in naphthalene. However, with the crystal orientation examined, only two are observed.

Over the whole region I_a/I_b is greater than unity. It follows, therefore, by analogy with the absorption spectrum, that the transition is short-axis polarized and the ^1L_a assignment is confirmed.

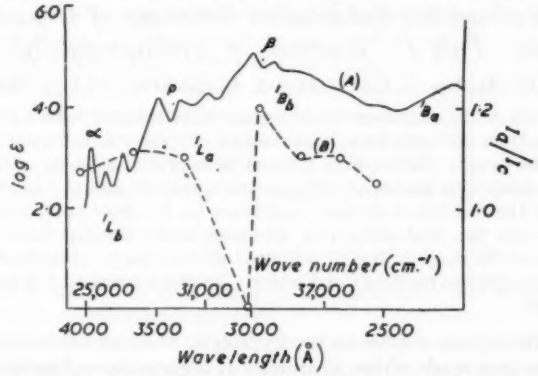
At wave numbers 33,000—39,000 *cm.*$^{-1}$. This region corresponds to a *b* polarized component of the most intense (Clar's β) transition to a ^1B_b–B_u upper state, analogous to the B_{3u} upper state 40,000 cm.$^{-1}$ in anthracene and 45,000 cm.$^{-1}$ in naphthalene (solutions). Such a transition is long-axis polarized, but the splitting would be sufficient to remove one component to the vacuum-ultraviolet region. In anthracene [14] the *a* component is removed and the *b* component remains in the crystal at about 37,000 cm.$^{-1}$. A similar phenomenon appears to occur in chrysene and the observed polarization is again *b* (from the I_b/I_a ratio). The electronic transition is accordingly to be assigned to ^1B_b after Platt, but considered to be split so that between 33,000 and 36,000 cm.$^{-1}$ only the *b* component appears in the crystal spectrum.

Pyrene.—The long axis runs through four carbon atoms, including the two central

[17] Clar, " Aromatische Kohlenwasserstoffe," Springer, Berlin, 1952, 2nd edn.
[18] Craig and Walsh, *J. Chem. Phys.*, 1956, **24**, 471.
[19] Fox and Schnepp, *ibid.*, 1955, **23**, 767.

atoms of this *peri*-condensed hydrocarbon. The crystal structure differs from that of anthracene, etc., in that the pyrene molecules occur in parallel pairs in the crystal. Such an arrangement of the molecules must cause a marked change in the Davydov splitting behaviour from that observed in the anthracene type crystal. If splitting is neglected, the oriented-gas model of the crystal predicts that in the (001) plane transitions polarized along the long molecular axis will give rise to $\varepsilon_a/\varepsilon_b = 5{\cdot}2$: short-axis transitions yield $\varepsilon_a/\varepsilon_b = 1{\cdot}0$ ($\varepsilon_a, \varepsilon_b$ denote extinction coefficients for light plane-polarized in a, b crystal directions); I_a/I_b is observed to be mostly greater than or equal to unity (Fig. 5) and this behaviour is therefore understandable in terms of the absorption spectrum. The first transition (Clar's α band) at 26,000 cm.$^{-1}$ has $I_a/I_b \approx 0{\cdot}8$, and the transition is therefore polarized along the shorter molecular axis. In terms of Platt's symbols, α bands are usually classed as ^1A–^1L_b, a transition which is [20] short-axis polarized in pyrene although long-axis in anthracene. (Pyrene and similar molecules are in a way a special case, as is indicated [21] by measurements of fluorescence polarization which give the same result for the first two transitions, a result not expected on the free-electron theory.)

FIG. 6. *Spectral dependence of the photocurrent from single crystals of* 1 : 2-5 : 6-*dibenzanthracene.*



A. Absorption spectra of solutions (as for Fig. 4, *C*, but without shift for change of phase).
B. Current ratio I_a/I_c. Spectral bandpass *ca.* 750 cm.$^{-1}$. Field direction along *c* axis. Field 1000 v/cm.

In the second transition (*p*-band) I_a/I_b shows an increase which may be explained by the presence of an *a* polarized region of absorption. As there is no evidence in the plot of I_a/I_b against frequency of a large splitting, the most likely explanation is that the *p*-band is polarized along the longer molecular axis. A transition to a ^1L_a state is [20] long-axis polarized in pyrene, although short-axis in anthracene, etc. Thus our result is compatible with free-electron theory, although it should be noted that since the increase in I_a/I_b is small, this transition could conceivably, like the first, be short-axis polarized.

In the region of the third transition (β band) and possibly also that of the fourth (β′ band), I_a/I_b is about unity, indicating a short-axis transition. A transition to a ^1B_b state is [20] long-axis polarized in pyrene.

In each of the first three transitions, therefore, the results are consistent with free-electron theory. The first transition is, however, only doubtfully so.

1 : 2-5 : 6-*Dibenzanthracene.*—The molecular symmetry is C_{2h} as in chrysene. Again, despite the lowering of symmetry, the α, *p*, β, and β′ bands appear, a fact which seems extraordinary on molecular-orbital theory, in which the upper states should all mix with a subsequent evening of intensity throughout the spectrum. This point has been discussed

[20] Ham and Ruedenberg, *J. Chem. Phys.*, 1956, **25**, 1.
[21] Williams, *J. Chem. Phys.*, 1957, **26**, 1186.

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by Moffitt.[22] On the oriented-gas model (no splitting) the crystal spectrum should show $\varepsilon_a/\varepsilon_c = 0{\cdot}001$ for a " long-axis " transition and $\varepsilon_a/\varepsilon_c = 4{\cdot}1$ for a " short-axis transition." For reasons given for chrysene, the x and y directions are degenerate; thus the terms " long-" and " short-axis " transition lose significance to an extent which seems greater in dibenzanthracene than in chrysene. This may well explain why I_a/I_c is moderately constant with frequency (Fig. 4). Owing to the difficulty of obtaining suitable sublimation flakes, experimental data were not extensive and are incomplete. The most that can be said is that there is a slight emphasis on a " short-axis " component about 34,300 cm.$^{-1}$.

Naphthalene and Phenanthrene.—These gave very small currents (see Table 1 of ref. 6). I_b/I_a is near to unity, possibly for the reason given earlier, although in the case of phenanthrene this ratio is near that of $\varepsilon_b/\varepsilon_a$.[23]

DEPARTMENT OF PHYSICAL CHEMISTRY,
THE UNIVERSITY OF SYDNEY,
SYDNEY, N.S.W., AUSTRALIA.

[*Received, March 25th,* 1957.]

[22] Moffitt, *J. Chem. Phys.*, 1954, **22**, 320.
[23] McClure, *ibid.*, 1956, **25**, 481.

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724. *Nucleophilic Substitution Reactions of Organosilicon Compounds. Part I. Reactions of Triisopropylsilyl Chloride.*

By A. D. ALLEN, J. C. CHARLTON, C. EABORN, and G. MODENA.

The rates of the reactions of tri*iso*propylsilyl chloride with alcohols and water in various solvents have been studied. Solvolytic rates vary greatly, being in the order: methanol > ethanol ≫ *iso*propyl alcohol. Comparison of the reactions with methanol (10%) in nitromethane and in dioxan solution shows that the reaction is strongly facilitated by the more polar solvent. In these solvents the first-order rate increases more rapidly than the concentration of the reagent, but in *iso*propyl alcohol the reaction is of the first order with respect to methanol and water. In this solvent an S_N2 mechanism is proposed.

THERE are no published rate studies on the hydrolysis of organosilicon chlorides. Kinetic investigations have been made of the hydrolysis of organosilicon fluorides [1] and hydrides,[2] and also the analogous condensations of silanols to siloxanes.[3] Generally steric hindrance and electron supply to the silicon atom depress the rate of these reactions. It has been suggested [1] that hydrolysis of the fluorides requires pre-equilibrium formation of an intermediate involving quinquecovalent silicon, which breaks down to give products in a rate-determining step. The data on which this suggestion are based can, however, be interpreted equally on the basis of an S_N2 reaction.[4]

The compound chosen for our initial investigation, tri*iso*propylsilyl chloride, was reported [5] as " resistant to hydrolysis by ordinary means." This overstates the stability of the compound towards hydrolysis, for conditions can be chosen in which the reaction proceeds at a convenient rate. Preliminary experiments indicated that the rate of solvolytic reactions in various alcohols varies greatly with the alcohol used. Relative rates at 0° are approximately: Pr^{i}OH 1, EtOH 10^3, MeOH 10^4.

Addition of small amounts of pyridine to these solutions displaced the equilibrium towards complete reaction, but had little effect on the rate. Since large changes of medium are involved in this comparison, a more detailed study of some reactions in inert solvents was made, including salt effects. With water as the reagent these reactions go

[1] Swain, Esteve, and Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 965.
[2] Baines and Eaborn, *J.*, 1956, 1436.
[3] Grubb, *J. Amer. Chem. Soc.*, 1954, **76**, 3408.
[4] Hughes, *Quart. Rev.*, 1951, **5**, 245.
[5] Gilman and Dunn, *Chem. Rev.*, 1953, **52**, 99; Gilman and Clark, *J. Amer. Chem. Soc.*, 1947, **69**, 1499.

substantially to completion, but with methanol an equilibrium is reached. Where necessary, initial rates were calculated to overcome this difficulty. The reactions were followed by quenching samples in a large excess of dry ether, in which the reaction is negligibly slow, and titrating the acid liberated with triethylamine in benzene. The results are shown in Table 1.

TABLE 1. *Reactions of triisopropylsilyl chloride with methanol and water in inert solvents at 25·1°.*

R_3SiCl (M)	MeOH (vol. %)	Et_4NX X	M	10^4k_2 (sec.$^{-1}$)	R_3SiCl (M)	ROH (vol. %)	Et_4NCl (M)	10^4k_1 (sec.$^{-1}$)
	In $MeNO_2$–MeOH					*In dioxan*		
0·03	5	—	—	1·65	0·01—0·02	MeOH (10)	—	0·04
,,	10	—	—	7·6	0·03	,, (10)	0·01	0·46
,,	10	Cl	0·01	10·5	,,	,, (22·5)	—	1·6
,,	10	ClO_4	0·01	9·0	0·01	H_2O (2)	—	2·9
,,	15	—	—	18·7	0·03	,, (3)	—	16·0
					,,	,, (4)	—	51
					0·01	,, (4·5)	—	90

Comparison of the results in nitromethane and dioxan shows that the reaction is strongly facilitated by the more polar solvent. The first-order rate coefficient increases more rapidly than the concentration of the reagent; this could be the result of a multiple order with respect to the reagent, or of a medium effect, or both. The greater reactivity of water than of methanol, as the reagent, is clearly shown by the results in dioxan. Salt effects are positive, and, as expected, are more pronounced in dioxan than in nitromethane. Variation of the initial concentration of the silicon halide does not affect the rate. In mixtures of the two solvents, with 10% of methanol as the reagent, a steady increase in the rate coefficient was observed as the nitromethane content was increased:

Solvent, nitromethane (%)	0	25	50	75	100
10^4k_1 (sec.$^{-1}$)	0·04	2·0	3·55	5·45	7·6

This solvent effect is similar to that observed for substitution at a carbon centre by the S_N2 mechanism when the reagent is neutral.

In order to clarify the problem of the high order with respect to the reagent, a study was made of the reactions in *iso*propyl alcohol. As we have seen, the solvolytic reaction in this alcohol is extremely slow, and it is possible to measure the reactions with small amounts of water and methanol against the background of the solvolysis. For the reaction with methanol the silicon halide was first allowed to react with the traces of water present in (dry) *iso*propyl alcohol before adding the reagent. The results are shown in Table 2.

TABLE 2. *Reactions of triisopropylsilyl chloride* (0·03M) *with methanol and water in isopropyl alcohol at* 25·1°.

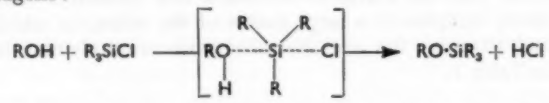
[MeOH] (M)	0	0·96	1·32	2·25	2·25	3·25	2·25[a]	2·25[b]
10^4k_1 (sec.$^{-1}$)	0·03	1·43	1·92	3·72	3·95	5·30	4·33	4·13
10^4k_2	—	1·49	1·45	1·65	1·75	1·63	1·92[a]	1·83[b]

[a] 0·11M-LiCl added. [b] 0·08M-$LiClO_4$ added.

$[H_2O]$ (M)	0	1·53	1·73	1·87	2·84	3·87	5·83
10^4k_1 (sec.$^{-1}$)	0·03	8·9	10·0	11·5	17·8	25·1	36·4
10^4k_2	—	5·8	5·8	6·15	6·25	6·5	6·25

The second-order rate coefficients, k_2, obtained by dividing the first-order coefficients by the initial concentration of the reagent, do not vary significantly over the range studied. Salt effects are small, positive, and independent of the nature of the anion. No autocatalysis by the hydrogen chloride liberated during the reaction was observed. From these results it is reasonable to assume that the high order with respect to the hydroxylic reagent in inert solvents is related to some property of the reagent which may be taken over by an (unreactive) hydroxylic solvent. Ignoring, for the time being, the rôle of the solvent, we

may postulate an S_N2 mechanism in which chloride is displaced directly in a one-stage process by the reagent :



In order to accommodate the depression of the rate of nucleophilic substitution reactions of silicon halides by electron supply to the silicon atom, it is only necessary to remember that, in an S_N2 reaction, the electron requirements depend on whether the bond-making or the bond-breaking process is the more important.[4, 6] For these reactions it appears that the emphasis is on the bond-making process, which is hindered by electron supply.

Experimental

Materials.—Alcohols were dried by reaction with magnesium or lithium, and fractionated through a 40 in. helix-packed column. Purity was checked by constancy of b. p. on change to total reflux. Nitromethane was shaken with anhydrous calcium sulphate and charcoal granules for several hours, run slowly through a 24 in. column of chromatographic alumina (dried at 350° for 6—8 hr.), and fractionated as above. To minimise decomposition this solvent was taken off under reduced pressure. If slight acidity was found in the distillate it was removed by re-passage through a short column of dried alumina. Purity was checked by conductivity not greater than 4×10^{-7} ohm^{-1} at 25°. Dioxan of " purified " grade was fractionated directly from sodium until the metal remained bright : it had m. p. ⩽ 11·6°. Ether and benzene were distilled from sodium. The water content of all " dry " solvents, and the concentration of water in aqueous reagent solutions, was checked by Karl Fischer titration.

Salts were of " AnalaR " grade, or prepared from " AnalaR " reagents, and were dried in vacuum over phosphoric oxide or magnesium perchlorate at suitable temperatures.

Tri*iso*propylsilyl chloride was prepared as previously described,[5] and had b. p. 80°/10 mm., n_D^{25} 1·4515. Its purity was checked by chloride titration.

Rate Measurements.—Reagent and solvent were mixed in a stoppered flask and brought to thermostat temperature. At zero time the tri*iso*propylsilyl chloride was added from a micro-pipette to the well-stirred solution. For the slower runs samples (5 or 10 ml.) were withdrawn by pipette at suitable time intervals and run into about 100 ml. of dry ether. The acid liberated was titrated with standard (0·01—0·05M) triethylamine in dry benzene, with neutral-red as indicator. For the faster runs an automatic pipette was used which enabled samples to be withdrawn at 30 sec. intervals. The reaction is virtually stopped in dry ether, no acidity being developed in the neutralised solution within 30 min. Infinity values were measured on several samples by adding aqueous alcohol to the ether solution (after initial titration as above) and titrating the total acid liberated.

E.g., tri*iso*propylsilyl chloride (0·03M) in 4% aqueous dioxan; 25°; titrated with 0·0371M-triethylamine in benzene :

Time (min.)	1·05	2·0	2·35	3·15	4·0	5·40	8·20	11·20	∞
Titre (ml.)	2·60	4·0	4·95	5·65	6·25	7·30	8·10	8·65	8·80

k_1 (graphically) $= 51 \times 10^{-4}$ sec.$^{-1}$.

For the reactions with methanol in *iso*propyl alcohol, the silyl chloride was added first to the *iso*propyl alcohol, and the solution was kept at thermostat temperature for about 3 hr. to complete any initial reaction with traces of water in the solvent. The acidity was then measured, and the methanol added at zero time.

E.g., tri*iso*propylsilyl chloride (0·03M) + methanol (2·25M) in *iso*propyl alcohol; 25·1° :

Time (min.)	0	1·00	3·00	4·40	9·20	14·10	20	31	60	∞
Titre (ml.)	3·25	3·35	3·55	3·75	3·97	4·48	4·80	5·30	6·16	8·20

k_1 (graphically) $= 3{\cdot}95 \times 10^{-4}$ sec.$^{-1}$.

William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, March 5th*, 1957.]

[6] Aŝperger and Ingold, *J.*, 1956, 2862.

725. *Nucleophilic Substitution Reactions of Organosilicon Compounds. Part II.*[1] *Reaction Mechanisms of Some Sterically Hindered Organosilicon Chlorides.*

By A. D. Allen and G. Modena.

A kinetic study has been made of the reactions of several sterically hindered trisubstituted silyl chlorides with alcohols, water, and chloride ion in various solvents. Orders of reactivity, both of the silyl chlorides and the reagents, indicate that steric hindrance is important. Generally a high order with respect to hydroxylic reagents is observed, and the reactions are facilitated by increasing polarity of the medium. At low (hydroxylic) reagent concentrations we observed autocatalysis, strong catalysis by added halide ion, and very low temperature coefficients. Hydrolysis of triphenylsilyl chloride catalysed by chloride ion is of first order with respect to both the chloride-ion and water concentrations. The rapid exchange reactions with ^{36}Cl in dioxan and nitromethane solutions follow second-order kinetics. The exchange reaction of triphenylsilanol with $H_2{}^{18}O$ in neutral 10% aqueous dioxan is very slow; in acid solutions the rate of reaction is increased. Possible mechanisms for these reactions are discussed, and an S_N2 type mechanism is proposed in which the reagent is associated with a basic molecule.

In order to obtain a more detailed picture of the mechanism of nucleophilic substitution of chlorine from organosilicon chlorides, the work described in the previous paper [1] was extended to include both less reactive and more reactive compounds.

Tri-1-naphthylsilyl Chloride.—This compound was reported [2] to resist hydrolysis in 5% aqueous acetone over a period of five days. We find that it is sparingly soluble in acetone, and in nitromethane, but that the reaction in 5% aqueous dioxan is rapid at room temperature. An investigation was made of the reactions with water and various alcohols in dioxan and butan-2-one, including the effect of adding salts (cf. Table 1).

Table 1. *Reactions of tri-1-naphthylsilyl chloride with alcohols and water in inert solvents at 25°.*

Solvent	R_3SiCl (M)	Reagent ROH	Vol. %	Salt	(M)	10^4k_1 (sec.$^{-1}$)
Dioxan	0·01	MeOH	22·5	—	—	0·44
,,	,,	H_2O	1·8	—	—	0·07
,,	,,	,,	4·5	—	—	5·2
COMeEt	0·05	MeOH	10	—	—	3·8
,,	,,	,,	10	$NaClO_4$	0·1	4·8
,,	,,	,,	10	LiCl	0·1	5·5
,,	,,	,,	25	—	—	55
,,	,,	Pr^nOH	10	—	—	0·21
,,	,,	,,	25	—	—	2·6
,,	,,	Hexanol	10	—	—	0·025
,,	,,	,,	25	—	—	0·19

The rates observed with this compound are slower than those found for tri*iso*propylsilyl chloride, but the same general pattern of behaviour is evident. Reactions are faster in the more polar solvent, but salt effects in butan-2-one solution are insignificant. Particularly noteworthy is the sensitivity to the nature and concentration of the reagent, ROH. These may be placed in order of efficiency: $H_2O \gg MeOH > Pr^nOH >$ hexanol $> Pr^iOH$.

The high reactivity of water, and the very low reactivity of *iso*propyl alcohol, may be due to steric factors. Changes in the basic strength of these alcohols may also be important. The specific rôle of hydroxylic molecules in the medium is illustrated clearly by the high

[1] Part I, Allen, Charlton, Eaborn, and Modena, preceding paper.
[2] Gilman and Brannen, *J. Amer. Chem. Soc.*, 1951, **73**, 4640.

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order with respect to the weakly polar hexanol in butan-2-one. This is despite the general reduction in polarity of the medium as the hexanol content is increased.

Tricyclohexylsilyl Chloride.—With this compound [3] steric hindrance to the approach of the reagent should be intermediate between that in the tri*iso*propyl and the tri-1-naphthyl compounds. A brief study was made in order to determine their relative reactivities. For the reactions in dioxan solution at 25·1° the following rate coefficients were measured: Methanol (22·5%), 1·45; Water (1·8%), 0·40; (4·5%), 17·0 (all 10^4k_1 in sec.$^{-1}$).

Triphenylsilyl Chloride.—This compound is very much more reactive than those previously studied. On steric grounds alone there should be little difference between this and the tri*iso*propyl compound. Its reactivity indicates that the polarisability of the phenyl groups strongly facilitates the formation of the transition state. With this compound it was possible to study the reactions with very low concentrations of the reagents. Under these conditions salt effects are considerable and autocatalysis is observed in many cases. The latter, together with a significant back-reaction, necessitated measurement of initial rates by extrapolation to zero time. Because of this an overall maximum error of about 10% must be allowed for these rate coefficients.

TABLE 2. *Hydrolysis of triphenylsilyl chloride* (0·01M) *in nitromethane at* 25·1°.

$[H_2O]$ (10^2M)	1·6	2·0	2·4	2·7	2·9	5·2	5·4	7·3	9·2	13·0
10^5k_1 (sec.$^{-1}$)	0·63	1·25	1·5	2·1	2·4	5·4	6·7	13·5	27	61
10^5k_2	0·40	0·61	0·63	0·78	0·83	1·05	1·25	1·85	2·9	4·7
Salt effects										
$[H_2O]$ (10^2M)	2·7	2·7	2·8	2·8	2·8	2·8	2·7	2·7	2·7	3·2
Et_4N^+ (10^4M) ClO_4^-	—	9	9 (Mg)	95	—	—	—	—	—	—
Et_4N^+ (10^4M) Br^- ...	—	—	—	—	1	4	—	—	—	—
Et_4N^+ (10^4M) Cl^- ...	—	—	—	—	—	—	0·45	3·4	9	9
10^5k_1 (sec.$^{-1}$)	2·1	2·2	2·6	3·7	12·5	37·5	10·5	59	95	120

In nitromethane (cf. Table 2), addition of tetraethylammonium perchlorate has a small effect on the rate, which may be interpreted as a simple salt effect. Substitution of magnesium for the cation does not alter this effect significantly. Halide ions, however, cause a very marked increase in rate; this catalysis may be related to the basic strength of the anion, since chloride is more effective than bromide. Unfortunately it was not possible to test this relation with more basic anions, since, in the low concentrations which must be used, the hydrogen chloride liberated would immediately convert them into their conjugate acids, and chloride-ion catalysis would be observed.

In dioxan the rate of hydrolysis is some 100 times shower than that in nitromethane

TABLE 3. *Hydrolysis of triphenylsilyl chloride* (0·01M) *in dioxan at* 25·1°.

$[H_2O]$ (M) ...	0·25	0·38	0·50	0·75	1·0	$[D_2O]$ (M)	0·45	0·68
10^5k_1 (sec.$^{-1}$)	0·33	1·95	7·25	85	1000	10^5k_1	2·2	26·5
10^5k_2	1·3	5·2	14·5	115	1000	k_1H/k_1D	2·0	1·9

Salt effects

Salt (10^4M)				10^5k_1	Salt (10^4M)				10^5k_1
$[Et_4N^+ClO_4^-]$	$[Et_4N^+Cl^-]$	[HCl]	$[HClO_4]$	(sec.$^{-1}$)	$[Et_4N^+ClO_4^-]$	$[Et_4N^+Cl^-]$	[HCl]	$[HClO_4]$	(sec.$^{-1}$)
0·5M-H_2O					0·38M-H_2O				
—	—	—	—	7·3	—	—	—	—	2·0
0·9	—	—	—	21	1·35	—	—	—	6·8
—	0·9	—	—	124	2·7	—	—	—	18
—	—	10	—	15	—	1·1	—	—	127
—	—	21	—	24·5	—	—	—	0·85	12·4
—	—	—	11	250	—	—	—	4·3	59
0·25M-H_2O									
—	—	—	—	0·33					
0·9	—	—	—	5·5					
—	1·0	—	—	76·5					

[3] Nebergall and Johnson, *J. Amer. Chem. Soc.*, 1949, **71**, 4022.

(cf. Table 3). Autocatalysis was observed, particularly with the lower concentrations of water used. Salt effects were even more marked, and the effect of added acid was studied. Substitution of deuterium oxide for water as the reagent reduced the rate by a factor or two.

In dioxan the increase in rate with increasing water concentration is very much more pronounced than that in nitromethane. This cannot be explained on the basis of a definite order with respect to the reagent. Obviously, changes due to the medium are very large in this weakly polar solvent. The dominating feature of the salt effects is again the strong catalysis by chloride ion. Since perchloric acid is more effective than tetraethylammonium perchlorate it seems that some electrophilic catalysis by the hydroxonium ion contributes to the reaction. The comparatively small effect of added hydrogen chloride shows (*a*) that the acid is virtually un-ionised in these media, and (*b*) that catalysis by associated hydrogen chloride is small. From this it follows that electrophilic catalysis by species other than the hydroxonium ion in the medium is not likely to be significant, and that the part played by any additional reagent molecules in the reaction is not electrophilic in character.

In an attempt to discover more precisely the nature of the chloride-ion catalysis, a more detailed study was made at various water concentrations, as reported in Table 4.

TABLE 4. *Hydrolysis of triphenylsilyl chloride catalysed by chloride ion in dioxan at* 25·1°

$[Et_4N^+Cl^-]$ (10^4M)	10^5k_1	10^5k_c	$k_2 = k_c/[Cl^-]$	$k_3 = k_2/[H_2O]$	$[Et_4N^+Cl^-]$ (10^4M)	10^5k_1	10^5k_c	$k_2 = k_c/[Cl^-]$	$k_3 = k_2/[H_2O]$
	0·5M-H_2O					0·25M-H_2O			
—	7	—	—	—	—	0·3	—	—	—
0·27	53	46	17	34	0·27	24	23·7	8·8	35
0·45	73	66	14	28	0·45	38	37·7	8·4	34
0·63	90	83	13	26	0·63	61	60·7	9·6	38
0·90	124	117	13	26	1·0	76·6	76·3	7·6	30
	0·38M-H_2O								
—	2	—	—	—					
0·36	49	47	13	35					
0·54	60	58	11	28					
1·10	127	125	11·5	30					

$k_c = k_1$ (catalysed) $- k_1$ (uncatalysed).

Two relations may be seen from these results: (*a*) for a given concentration of water, the increment of rate due to catalysis (k_c) is proportional to the chloride-ion concentration, and (*b*) the values of k_2 so obtained are proportional to the water concentration. The third-order coefficient, k_3, is reasonably constant over the range of concentrations studied. Thus, for the overall reaction, a rate equation may be written as:

$$\text{Rate} = k_{1(H_2O)}[R_3SiCl] + k_3[R_3SiCl][H_2O][Cl^-]$$

where $k_{1(H_2O)}$ is the first-order rate coefficient for the uncatalysed reaction at a given water concentration.

Temperature-dependence.—A qualitative study of the effect of temperature on some of these reactions is summarised in Table 5.

TABLE 5.

R in R_3SiCl	Solvent	Reagent: ROH	Reagent: Vol. %		Temperature: 0°	9·8°	25°	45°	60°
Pr^i	Pr^{i}OH	H_2O	[a]	10^2k_2 =	2·0	3·6	6·0	—	—
,,	$MeNO_2$	MeOH	10	10^4k_1 =	4·3	5·4	7·6	—	—
,,	Dioxan	H_2O	2	10^4k_1 =	—	—	2·6	2·9	—
,,	,,	MeOH	10	10^4k_1 =	—	—	3·7	4·8	—
1-$C_{10}H_7$	,,	H_2O	2	10^5k_1 =	—	—	0·9	—	1·2
Ph	,,	,,	0·9	10^5k_1 =	—	—	7·3	9·6	—
,,	,,	,, [b]	0·9	10^5k_1 =	—	—	73	88	—

[a] $[H_2O]$ between 0·01 and 0·05M. [b] $[Et_4N^+Cl^-]$ ($0·4 \times 10^{-4}$M) added.

It will be seen that the temperature-dependence varies with the medium used. In *iso*propyl alcohol a " normal " temperature coefficient is obtained. In nitromethane or dioxan with 10% of methanol, temperature is less important, and in these solvents with small water concentrations very small coefficients are observed. It is noteworthy that a similar dependence on temperature is shown by both the uncatalysed and the chloride-catalysed hydrolysis of the phenyl compound, despite the ten-fold rate factor. Such small temperature coefficients are generally associated with complex reactions, particularly those involving two or more stages. In our results there is a correlation between small temperature coefficients and high reaction order, both of which are consistent with a complex reaction. The only reactions showing simple second-order kinetics, *i.e.*, those in *iso*propyl alcohol solution, also have normal temperature coefficients.

TABLE 6. *Chloride-exchange reactions* at 25·1°.

Solvent		R in	$[R_3SiCl]$	$[Et_4NCl]$	k_2
Dioxan (%)	$MeNO_2$ (%)	R_3SiCl	(10^3M)	(10^3M)	(sec.$^{-1}$ mole^{-1} l.)
0	100	Pr^i	0·83	1·2	7
		,,	0·98	1·8	6·5
25	75	,,	0·65	0·58	10·4
		,,	0·75	0·98	12·5
		,,	0·61	1·9	11
		,,	0·80	0·64	11·2 [a]
50	50	,,	0·82	0·61	17
		,,	0·85	0·99	17
75	25	,,	0·80	0·61	16·5
		,,	0·79	1·0	15·6
50	50	1-$C_{10}H_7$	0·67	0·64	43
		,,	0·63	1·24	43
		,,	0·64	1·19	41
75	25	,,	0·71	0·77	18
		,,	0·47	0·69	22
50	50	*cyclo*Hexyl	0·40	0·22	5·4
		,,	0·41	0·88	4·6

[a] $[Et_4NClO_4]$ (0·01M) added.

Halogen-exchange Reactions.—Expecting that the chemical simplicity of halogen-exchange reactions might help to clarify the mechanism of these substitution reactions, we studied several exchange reactions, using ^{36}Cl-labelled tetraethylammonium chloride, with mixtures of dioxan and nitromethane as solvents (see Table 6).

Qualitative measurements with triphenyl- and trimethyl-silyl chloride in the 1 : 1 solvent mixture indicated complete reaction within 0·3 second.

Good second-order kinetics were observed with all the compounds in all the solvents used. The order of reactivity towards chloride ion is different from that towards the hydroxylic reagents, being tri-1-naphthyl > tri*iso*propyl > tri*cyclo*hexyl. Steric factors may be less important with this small reagent, and dispersion of its negative charge will be facilitated by the polarisability of the naphthyl groups. Effects of the medium are small, the rate increasing with increasing dioxan content up to the 1 : 1 mixture. At higher dioxan contents the rate decreases again, possibly owing to association of the ionic species in such weakly polar media. The addition of tetraethylammonium perchlorate does not affect the rate.

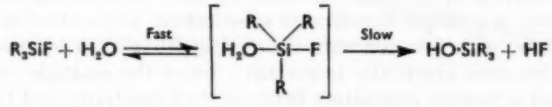
DISCUSSION

The more important features of our results may be summarised as follows: (*a*) The orders of reactivity, both of the silicon chlorides and of the reagents used, indicate that steric hindrance is important in these reactions. (*b*) Aryl groups (phenyl and naphthyl) facilitate the reactions, particulatly with chloride ion as the reagent. (*c*) Polarity of the medium increases the rate of reaction with neutral reagents, and depresses slightly the

rate with negatively charged reagents. (*d*) In inert solvents the order with respect to hydroxylic reagents is always greater than one, but reactions in hydroxylic solvents are of first order with respect to these reagents. (*e*) In inert solvents, with low concentrations of hydroxylic reagents, strong catalysis by halide ions, together with low temperature coefficients, is observed. In *iso*propyl alcohol, temperature coefficients are normal and no catalysis by halide ion is observed. (*f*) Hydrolysis catalysed by chloride ion is of first order with respect to both halide ion and water. Chloride-ion exchange is of first order with respect to chloride ion.

Possible Reaction Mechanisms.—(1) *Unimolecular ionisation.* Since silicon is more electropositive than carbon, it might be expected that ionisation to give a siliconium ion would occur. So far, however, there is no evidence of such a process. Flowers, Gillespie, and Robinson [4] have carried out cryoscopic and conductivity measurements with several silanols in sulphuric acid, and shown that siliconium ion is not formed, at least to any measurable extent, in that solvent. Carbonium ions are stabilised by resonance between structures involving double-bond formation, and it was hoped that the structure of tri-1-naphthylsilyl chloride would be particularly suitable in this respect. Our failure to observe this mechanism with this compound seems to indicate that ionisation mechanisms, so frequently observed in organic compounds, do not occur in organosilicon compounds.

(2) *Formation of quinquecovalent silicon intermediates.* For the hydrolysis of triphenyl- and tri-*p*-tolyl-silyl fluoride in aqueous acetone, the rapid pre-equilibrium formation of a quinquecovalent intermediate, followed by its rate-determining unimolecular breakdown, has been proposed : [5]



The formation of stable or semi-stable compounds in which silicon has a covalency greater than four is well established with the fluoro- and chloro-silanes.[6] When one or more organic groups are attached to silicon, however, there is no evidence of further co-ordination. Eaborn [7] has shown that the ultraviolet absorption spectra of pyridine and *p*-toluidine in several organosilicon solvents do not differ significantly from the spectra in hexane. This indicates that, even under very favourable conditions, with little steric hindrance, no measurable co-ordination to silicon by these strong reagents occurs.

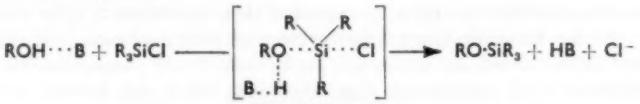
The simple kinetic form of the reaction cannot distinguish between a synchronous bimolecular process and a pre-equilibrium as proposed by Swain *et al.*[5] These authors considered both possibilities and decided in favour of the latter on the grounds that electron supply hinders the reaction, and that silyl fluorides are hydrolysed more slowly than the corresponding silyl chlorides. It has already been pointed out that depression of the rate by electron supply is consistent with certain S_N2 reaction mechanisms,[1] and it is well known that, under S_N2 conditions, organic fluorides are hydrolysed more slowly than the corresponding chlorides.[8] It is not possible to distinguish between the alternative mechanisms on this basis.

There are several objections to this type of mechanism for the reactions we have studied : (*a*) The unimolecular breakdown of the complex should be subject to general electrophilic catalysis. We have seen that, although there is slight catalysis by hydroxonium ion, other species, including hydrogen chloride, are ineffective. In particular, the high order with respect to hydroxylic reagents cannot be explained on the basis of electrophilic attack. (*b*) Steric hindrance is very great with these compounds :

[4] Personal communication from Dr. R. J. Gillespie.
[5] Swain, Esteve, and Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 965.
[6] Stone and Seyferth, *J. Inorg. Nuclear Chem.*, 1955, **1**, 112.
[7] Eaborn, *J.*, 1955, 2047.
[8] Chapman and Levy, *J.*, 1952, 1673.

e.g., tri*iso*propylsilyl chloride does not react with *iso*propyl-lithium to give tetra*iso*propylsilane.[9] Hence a kinetically rapid formation of the complex seems unlikely. (*c*) Such a pre-equilibrium would involve complete reaction for the symmetrical chloride exchange. Although the exchange is rapid, it is not kinetically " fast." Similarly we find that the exchange between $H_2{}^{18}O$ and triphenylsilanol is extremely slow in neutral 10% aqueous dioxan. This reaction is acid-catalysed, and work is in progress on the detailed kinetics. (*d*) It is difficult to accommodate chloride-ion catalysis in such a mechanism.

Proposed Reaction Mechanism.—The simplest scheme which can accommodate all the observed results is as follows :



(Transition state)

The hydrogen-bonded association ROH · · B may be formed in a fast pre-equilibrium step, or it could occur during the approach of the reagent to silicon. B is any entity which can act as a base, *e.g.*, H_2O, ROH, halide ion. In this scheme the importance of the association in the reaction sequence is that the reagent is unable to displace chlorine unless a base is available to accept the proton. In hydroxylic solvents the latter process is unimportant, since all the reactants and transition state are highly solvated, and the proton transfer is kinetically fast. For this reason, although addition of traces of pyridine displaces the equilibrium in alcoholic solvents, no basic catalysis is observed. In such solvents the reaction is a simple bimolecular substitution, as we observe.

In inert solvents, with low concentrations of hydroxylic molecules, transfer of the proton to a base becomes kinetically important; hence the multiple order with respect to the reagent, and a possible correlation between their reactivity and basicity. At very low concentrations of hydroxylic species solvation of added halide ions will be low, and hence their basic properties will be enhanced. Consistently their catalytic effect falls off very rapidly as the concentration of solvating molecules increases, and a simple salt effect, similar to that of the perchlorate ion, is observed in more highly solvating media.

The small temperature coefficients observed at low concentrations of hydroxylic molecules would result from the decrease in concentration of the hydrogen-bonded complex as the temperature is increased. The first-order dependence on water concentration in the presence of chloride ion is strong evidence in favour of this mechanism. The reduction in rate by a factor of two when deuterium oxide is used in place of water as the reagent is consistent with a proton transfer involved in the transition state.

Somewhat similar schemes have been proposed for the acid- and base-catalysed hydration of acetaldehyde,[10] and for the alcoholysis of acid chlorides in inert solvents.[11]

Experimental

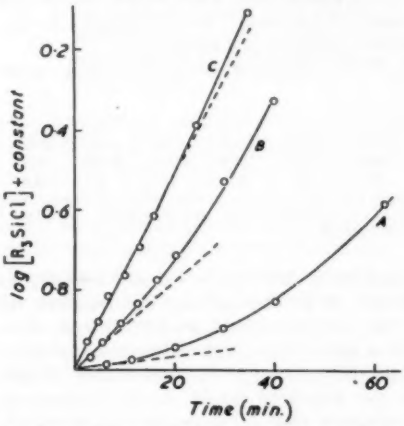
Materials.—Solvents, reagents, and salts were prepared and dried as described in Part I. The silyl chlorides have been previously reported. Physical properties of the products used were : tri-1-naphthylsilyl chloride, m. p. 210° (from light petroleum); tri*cyclo*hexylsilyl chloride, m. p. 102°, b. p. 156°/0·7 mm.; triphenylsilyl chloride, " purified " grade, redistilled, b. p. 161°/0·6 mm.; trimethylsilyl chloride, " purified " grade, used as supplied.

Rate Measurements.—These were carried out as described in Part I, except as follows. The solid silyl chlorides and the reagents were dissolved separately in two portions of the solvent, brought to thermostat temperature, and mixed at zero time. For runs at 45° and 60° sealed Pyrex glass tubes were used, which were crushed under dry ether at room temperature; titration

[9] Gilman and Clark, *J. Amer. Chem. Soc.*, 1947, **69**, 1499.
[10] Bell, Rand, and Wynne-Jones, *Trans. Faraday Soc.*, 1956, **52**, 1093; Bell and Darwent, *ibid.*, 1950, **46**, 34.
[11] Hudson and Saville, *J.*, 1955, 4121.

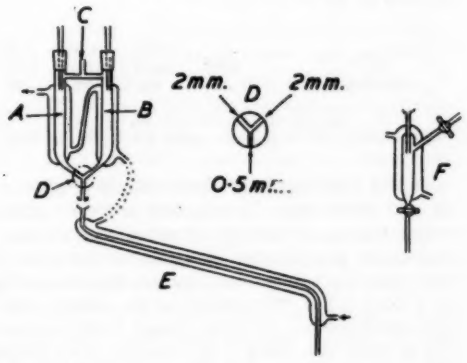
was as before. It was observed that, if these samples were " killed " by freezing at −80°, very high acid values were obtained, in some cases amounting to an additional 50% of the total reaction. It appeared that considerable reaction was occurring during the melting and freezing. Generally, first-order rate constants were calculated from the initial slope of the first-order log plot, and second-order constants by dividing the first-order constant by the initial concentration of the reagent, which was nearly always in large excess. For those runs which were free from autocatalysis and went to completion, good first-order kinetics were observed throughout.

FIG. 1. *Hydrolysis of triphenylsilyl chloride (0·01M) in 1% aqueous dioxan at 25°.*



A, Run without added salt, showing autocatalysis. *B*, Effect of addition of tetraethylammonium chloride ($0·27 \times 10^{-4}$M). *C*, Effect of addition of tetraethylammonium chloride ($0·63 \times 10^{-4}$M), showing almost complete elimination of autocatalysis.

FIG. 2. *Apparatus used for the measurement of very fast chloride-exchange.*



E.g., tri-1-naphthylsilyl chloride (0·005M) in 10% methanolic butan-2-one, at 25·1°; triethylamine = 0·053M :

Time (min.)	2	6	10	15	20	33	45	60	90	∞
Titre (ml.)	0·41	1·25	1·90	2·75	3·45	4·9	6·05	7·05	8·2	9·43
10^4k_1 (sec.$^{-1}$)	3·8	3·55	3·76	3·7	3·8	3·7	3·8	3·83	3·8	—

A series of runs in which autocatalysis and salt effects were observed are shown in Fig. 1. These show clearly the catalysis by halide ion, accompanied by depression of the autocatalysis as the halide-ion concentration is increased.

Chloride-exchange Reactions.—For these reactions, which involved measurements within 1 second in some cases, the flow apparatus shown in Fig. 2 was used.

Samples of exactly equal volume (from two automatic pipettes) were placed in the jacketed arms *A* and *B*. One of these contained the silyl chloride and the other the ^{36}Cl-labelled tetraethylammonium chloride. A (measured) pressure of nitrogen was exerted equally on the samples *via* the inlet *C*. A reservoir (5 l.) and adjustable fine leak were used to maintain constant pressure during each measurement. Water at 25° was circulated continuously through all the jackets. After 20 min., when temperature equilibrium had been established, the tap *D* was fully opened (at zero time) and the reactants were forced through the reaction tube *E* into 100 ml. of sodium-dried ether contained in a No. 4 sintered-glass filter funnel. The time *t'* for total outflow of the liquid was recorded. The salt was precipitated immediately on contact with the ether. As soon as outflow ceased, suction was applied to a Buchner flask below the filter, and the salt was separated from the solvent within 5 seconds of precipitation. After the salt had been washed with several small amounts of dry ether, it was dissolved in

approximately 15 ml. of distilled water and set aside for counting and potentiometric titration of chloride with silver nitrate solution. Reaction times were varied both by changing the pressure and by the use of several reaction tubes (E) of different volumes. The reaction time (t) is given by: $t = t' \times v/V$, where t' = measured time of total outflow, v = volume of the reaction tube, and V = total volume of the reaction solutions. Hence if the ratio v/V is small (in our apparatus 0·1—0·03) very short reaction times can be measured accurately. For the longer reaction times, and for infinity values, a reservoir F was used in place of the reaction tube. Good agreement was found between the two systems when it was possible to duplicate reaction times by both methods. A ball-and-socket joint facilitated changes of the reaction vessel, and proved to be leakproof under pressure. The efficiency of the "killing" of the reaction by precipitation of the salt was checked by dispensing with the reaction vessels and running the mixed samples directly on to the ether from the ball joint. Such tests gave 1—2% reaction, which is approximately correct for the time of contact of the solutions.

E.g., tri-1-naphthylsilyl chloride (0·0063M) + $Et_4N^+{}^{36}Cl^-$ (0·0124M) *in* 50 : 50 *dioxan* : *nitromethane at* 25°.

t (sec.)	0	0·39	0·70	0·75	0·90	0·99	1·13	2·01	2·55	3·61
$(C - X)$ *	9002	8409	8106	7971	7668	7582	7296	6767	6540	6255
k_2 (sec.$^{-1}$ mole^{-1} l.)...	—	46	37	39	43	42	47	43	43	49

* C = Initial specific count for $Et_4N^+Cl^-$; $(C - X)$ = specific count for $Et_4N^+Cl^-$ at time t (measured); X = specific count for R_3SiCl at time t (calculated).

$H_2{}^{18}O$ *Exchange.*—Triphenylsilanol (2 g.) was dissolved in dry dioxan (90 ml.) with $H_2{}^{18}O$ (10 ml.) (1·07 atom % enriched in ^{18}O). After 24 hr. at 25° the solvent was removed by evaporation in a vacuum at room temperature. The solid was dried at 50°/0·1 mm. over magnesium perchlorate. Portions of the solid, with a little ammonium chloride as catalyst, were sealed in a (measured) carbon dioxide atmosphere in Pyrex ampoules, and heated at 250° for 7 days. The ^{18}O content of the carbon dioxide was measured (by Dr. C. A. Bunton) by mass-spectrometer, and was found to be normal, indicating that no exchange had occurred. The method was checked by starting with prepared triphenylsilanol containing 1·07 atom % excess of ^{18}O, which was allowed to react with normal water exactly as above. On analysis the carbon dioxide was found to contain 1·06 atom % excess of ^{18}O, due allowance being made for dilution, confirming the absence of exchange.

The same reactions were carried out, with normal triphenylsilanol and 1·07 atom % enriched water, in the presence of (*a*) 0·1M-hydrochloric acid and (*b*) 0·1M-perchloric acid. After 3 hr. at 25° the silanol was precipitated by adding normal water, washed with small amounts of water to remove traces of acid, and dried as before. On analysis the carbon dioxide contained (*a*) 0·54 and (*b*) 0·47 atom % excess of ^{18}O, indicating that considerable exchange had taken place in both cases.

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William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1.

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726. *The Oxides of Uranium. Part VIII.* The System Uranium Dioxide–Yttria.*

By I. F. Ferguson and P. G. T. Fogg.

The mixed-oxide system UO_2–Y_2O_3 has been investigated by *X*-ray powder techniques. A range of solid solutions, with pseudo-fluorite structures, exists between 0 and 78 moles % of $YO_{1\cdot5}$, whose cell constant is a non-linear function of composition. Between 78 and 96 moles % of $YO_{1\cdot5}$ there is an immiscibility gap. Beyond 96 moles % of $YO_{1\cdot5}$ a solid solution range occurs based upon the Tl_2O_3 structure. Density measurements show that all these solid solutions have an anion-vacancy structure. Samples were prepared and handled *in vacuo*, as they absorb oxygen at room temperature.

The structures of uranium dioxide and yttria are related. Uranium dioxide has a fluorite-type lattice with a cube-cell edge of 5·457 *kX*; yttria has a larger cubic unit cell of the Tl_2O_3 type, with an edge of 10·585 *kX*. The structure of yttria can be considered in terms of a fluorite pseudo-cell, with an edge of 5·293 *kX*, in which the tervalency of yttrium causes an ordered omission of oxygen from the anion sub-lattice. These oxides' structural and dimensional similarity makes it likely that they will form anomalous solid solutions. This possibility was therefore investigated, extending the work of Anderson *et al.* on uranium dioxide to include a related mixed oxide with a defective anion sub-lattice.

Anderson, Burden, and Johnson [1] showed that solid solutions with the fluorite structure could be prepared by heating the mixed oxides at 2000° c *in vacuo*. Anderson, Ferguson, and Roberts [2] showed that such preparations were oxidised rapidly in air at room temperatures. The existence of a wide range of fluorite-type solid solutions in this system was confirmed by Hund *et al.*[3] None of these determined the oxygen content of the preparations and it appears [4,5] that their samples were oxidised, and not typical of the system uranium dioxide–yttria. We prepared mixed crystals containing uranium(IV) and anion defects by an already proved method,[2,5] and examined them by *X*-ray diffraction. Ferguson and Roberts [5] have studied corresponding mixed crystals in the system U–Y–O in which the anion sub-lattice is intact and the uranium valency exceeds 4. These studies confirm and extend the results of Hund and his co-workers.

Experimental

Materials.—Pure uranium oxide was used. Yttria, purchased from New Metals and Chemicals, Ltd., London, was shown spectroscopically to be 99·99% pure.

Preparation.—The rapid oxidation of samples in air at room temperature necessitated their preparation by a technique with use of a uranium getter, followed by manipulation in a vacuum. The mixed crystals were prepared by co-precipitating the hydroxides from solutions containing known amounts of yttrium and uranyl nitrates by addition of excess of carbon dioxide-free aqueous ammonia. The precipitate was decomposed at 375° c, partially reduced by heating it overnight at 1400° in a stream of carbon monoxide, then made into a pellet and heated to 2000° *in vacuo*. These ignitions increased the crystallite size and thus improved the final *X*-ray diffraction photographs. The product was finely ground and reduced *in vacuo* by heating it with clean, cast uranium at 950°—1050° in a sealed, evacuated silica tube. A silica jacket around this tube was evacuated continuously to minimise diffusion of gases into the reaction vessel. After an arbitrary heating time (1—3 days) the sample was shaken into an attached ball-mill, ground, and then shaken into *X*-ray capillaries and the density holder.

* Part VII, *J.*, 1955, 3946.

[1] Anderson, Burden, and Johnson, 1951, unpublished work.
[2] Anderson, Ferguson, and Roberts, *J. Inorg. Nuclear Chem.*, 1955, **1**, 340.
[3] Hund, Peetz, and Kottenhahn, *Z. anorg. Chem.*, 1955, **278**, 184.
[4] Ferguson, Thesis, London, 1956.
[5] Ferguson and Roberts, unpublished work.

XUM

X-Ray Measurements.—Samples, contained in evacuated, 0·3 mm. diameter, thin-walled, Pyrex capillaries, were examined in 19 cm. Unicam Debye–Scherrer cameras. Nickel-filtered Cu-K_α radiation was used; λ_{α_1} was assumed to be 1·537396 *kX*, and λ_{α_2} 1·541232 *kX*. Cell constants were obtained by extrapolation to $\theta = 90°$ by use of Nelson and Riley's method.[6] The accuracy of measurement of the cube cell edge depends upon the degree of crystallinity of the sample, and errors are quoted as recommended by Henry, Lipson, and Wooster.[7]

Density.—Sample volumes were determined by measuring the displacement of a known volume of helium. This method [8] does not expose samples to the air; the sample is contained in a tube sealed by a waxed-in plunger, which is opened by softening the wax with a low helium pressure on the outside. The measured densities were consistent to about 0·05 g./c.c.

Results and Discussion

Under our conditions of preparation, the system uranium dioxide–yttria contains two solid solution ranges separated by an immiscibility gap. One solid solution range extends from 0 to 65 moles % of $YO_{1·5}$ and is based upon the fluorite lattice, the other extends from 96 to 100 moles % of $YO_{1·5}$ and is based upon a Tl_2O_3-type lattice. The measured cell edges of samples are given in Table 1.

The properties of the solid solutions with pseudo-fluorite lattices vary continuously with composition. It is however convenient to consider different composition ranges separately. From 0 to 25 moles % of $YO_{1·5}$ there is a nearly linear relation between the cell edge and composition of samples. Brauer and Gradinger [9] suggested that this relation may be extrapolated to 100% $YO_{1·5}$ to give a value corresponding to an unknown modification of yttria with a pseudo-fluorite structure. From a series of extrapolations in related mixed-oxide systems these workers have suggested the relation:

$$a_f = 0·78705\ (a_c/2) + 1·226\ (\text{in } kX)$$

where a_c is the observed cell edge of an oxide with the Tl_2O_3 structure, and a_f is the extrapolated value corresponding to its hypothetical pseudo-fluorite form. We find an extrapolated value of 5·398 *kX*, which agrees well with the value 5·391 *kX* calculated from the above formula. A similar value of 5·393 *kX* is obtained from the system ceria–yttria.[10]

Beyond 25 moles % of $YO_{1·5}$ the relation between cube cell edge and composition departs from linearity, but the slope of the curve is continuous and not as suggested earlier.[2] *X*-Ray powder photographs of compositions between 0 and 50 moles % of $YO_{1·5}$ show that these solid solutions have pseudo-fluorite structures. However, beyond 50 moles % of $YO_{1·5}$ additional faint reflexions appear which correspond to a transition from a pseudo-fluorite to a Tl_2O_3 structure. This transition is not, however, continuous and an immiscibility gap appears between 78 and 96 moles % of $YO_{1·5}$. From 96 to 100 moles % of $YO_{1·5}$ there is a narrow solid-solution range based upon the Tl_2O_3 structure.

At 76·3 moles % of $YO_{1·5}$ an unidentified phase was prepared, but no attempts were made to determine the composition range over which it is stable.

Formation of solid solution between these oxides may involve one of two mechanisms. To maintain a charge balance in the crystal, either vacancies must appear on the anion sub-lattice or excess of cations must be accommodated on interstitial positions. A comparison of the measured densities (Table 2) with those calculated on the basis of the above models indicates that these solid solutions contain vacancies on the anion sub-lattice. The measured densities are about 0·2 g./c.c. lower than those calculated; similar discrepancies have been discussed by others.[11]

[6] Nelson and Riley, *Proc. Phys. Soc.*, 1945, **57**, 160.
[7] Henry, Lipson, and Wooster, "The Interpretation of *X*-Ray Diffraction Photographs," Macmillan and Co., London, 1951, p. 191.
[8] Anderson, Harper, Moorbath, and Roberts, 1952, A.E.R.E. Report C/R 886.
[9] Brauer and Gradinger, *Naturwiss.*, 1951, **24**, 559.
[10] Martin, personal communication.
[11] Anderson, Edgington, Roberts, and Wait, *J.*, 1954, 3324.

TABLE 1. *Composition, cube cell edge and lattice type of preparations.*

(All cube cell edges are quoted in terms of a fluorite cell, or sub-cell.)

Composition (moles % of $YO_{1\cdot5}$)	Cube cell edge (kX)	Lattice type	Composition (moles % of $YO_{1\cdot5}$)	Cube cell edge (kX)	Lattice type
0·00	5·457 ± 0·001	Fluorite	70·0	5·365 ± 0·005	Fluorite
10·1	5·451 ± 0·001	,,	70·1	5·349 ± 0·002	,,
15·0	5·449 ± 0·003	,,	71·2	5·352 ± 0·005	,,
20·7	5·441 ± 0·001	,,	75·0	5·366 ± 0·005 5·332 ± 0·005	See †
29·4	5·437 ± 0·005	,,	76·3	—	Unknown phase
30·0	5·436 ± 0·005	,,	79·5	5·335 ± 0·002	Fluorite
33·8	5·4250 ± 0·0005	,,	81·1	5·35 ± 0·01	,, *
38·6	5·422 ± 0·002	,,	87·0	5·338 ± 0·002 Fluorite 5·294 ± 0·002 Tl_2O_3	2 phase
40·0	5·417 ± 0·002	,,	90·0	5·341 ± 0·005 Fluorite 5·303 ± 0·002 Tl_2O_3	2 phase
47·4	5·405 ± 0·005	,,	93·8	5·301 ± 0·002	Tl_2O_3
50·0	5·400 ± 0·002	,,	95·9	5·301 ± 0·001	,,
55·0	5·391 ± 0·003	,, *	98·2	5·2950 ± 0·0005	,,
59·6	5·384 ± 0·005	,,	100·0	5·2925 ± 0·0005	,,
60·9	5·375 ± 0·003	,,			
63·8	5·37 ± 0·05	,,			
65·0	5·367 ± 0·005	,,			

* The X-ray film exhibits a background of faint Tl_2O_3-type reflexions.
† Two coexisting fluorite phases. The sample was prepared in duplicate.

TABLE 2. *Comparison of calculated and observed densities.*

Composition (moles % of $YO_{1\cdot5}$)	Cube cell edge (kX)	Theor. density (g./c.c.) on the basis of Anion vacancies	Interstitial cations	Measured (g./c.c.)
10·1	5·451 ± 0·001	10·36	10·63	10·01 ± 0·07
20·7	5·441 ± 0·001	9·74	10·27	9·46 ± 0·05
47·4	5·405 ± 0·005	8·18	9·28	8·09 ± 0·04
59·6	5·384 ± 0·005	7·46	8·77	7·57 ± 0·07
70·1	5·349 ± 0·002	6·83	8·36	6·85 ± 0·05
79·5	5·335 ± 0·002	6·31	7·87	6·01 ± 0·02
90·0	5·303 ± 0·002	5·69 *	7·35 *	5·39 ± 0·05

* Calc. on the basis of the Tl_2O_3 phase.

We could not determine whether our preparations are thermodynamically stable at room temperature. The cation distribution in samples may be characteristic of temperatures as high as 2000°, but the distribution of the more mobile anions is probably typical of temperatures below 1000°. Slight variations in preparative conditions may alter the distribution of ions in samples and explain the confusion in the measured cell constants between 65 and 78 moles % of $YO_{1\cdot5}$. We have been unable to decide whether the latter region represents an extension of the pseudo-fluorite solid solution range or not.

Preparations containing less than about 55 moles % of $YO_{1\cdot5}$ are oxidised rapidly in air at room temperature, changing abruptly from brown to black, and the unit cell of the crystal contracts as the uranium valency rises above four. The oxidation probably involves a rapid diffusion of oxygen anions through the anion sub-lattice. A similar diffusion must accompany the reduction of samples by uranium. The mobility of oxygen in the fluorite lattice has already been noted in uranium dioxide, but there the oxygen enters interstitital positions.

We thank the Spectroscopic Group at A.E.R.E. for the analysis of yttria.

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727. *Cyclitols. Part VI.* The Hydrogenation of Hexahydroxybenzene.*

By S. J. Angyal and D. J. McHugh.

Catalytic hydrogenation of hexahydroxybenzene under various conditions gave complex mixtures of polyhydroxy*cyclo*hexanes which were separated by chromatography on cellulose powder. Seven inositols and four quercitols were obtained from various runs, including the previously unknown *cis*-inositol, *cis*quercitol, and *cis*inosose. At room temperature with a palladium catalyst *myo*inositol is the main product, whereas palladium-on-carbon yields mainly *cis*-inositol. High-temperature hydrogenation over Raney nickel shows little stereospecificity.

The first synthesis of an inositol was reported by Wieland and Wishart [1] who catalytically hydrogenated hexahydroxybenzene with a palladium catalyst at room temperature and atmospheric pressure. They obtained the biologically important *myo*inositol in a yield of over 50%. Such a high yield of one isomer—out of a possible eight—was tentatively explained by postulation of the all-*cis*-configuration for *myo*inositol; but since it is now known that *myo*inositol is the 1235/46-isomer, this reaction constitutes a remarkable instance of stereospecificity.

Two attempts to repeat this work, with platinum and palladium catalysts at various temperatures, failed.[2,3] Anderson and Wallis,[3] however, hydrogenated hexahydroxybenzene with Raney nickel at 125—150°/100 atm., the products ranging from *cyclo*hexanediols to inositols. Five cyclitols, including *myo*inositol, were isolated in small yield by tedious crystallisation and by fractional distillation of the acetates; the identity of these compounds will be discussed below.

In 1949, Kuhn, Quadbeck, and Röhm [4] confirmed Wieland and Wishart's original report by carrying out hydrogenations both at 50—55° and at 20°; though the reaction was slower at 20° the yield was better, being 35% of crude inositol from which pure *myo*-inositol was isolated in 13% yield. The authors recognised that the crude product represented a mixture of cyclitols but did not attempt to separate them. An improvement introduced by Kuhn *et al.* was the use of the stable and readily prepared tetrahydroxybenzoquinone as starting material instead of hexahydroxybenzene, which is difficult to purify owing to its rapid aerial oxidation. In the course of the hydrogenation the quinone is readily converted into hexahydroxybenzene.

The development of cellulose-powder chromatography as a convenient method for the separation of cyclitols [5] made it possible to investigate the products formed in the hydrogenation of hexahydroxybenzene under different conditions. A preliminary account of our results has been published.[6]

Under the conditions given by the German authors,[4] tetrahydroxybenzoquinone took up hydrogen, rapidly for the first mol., then very slowly; several additions of catalyst were needed to complete the reaction. Paper chromatography [7] (in acetone–water, 4 : 1 v/v) showed that a large number of compounds had been formed, some of which moved too rapidly to be inositols. By a combination of cellulose-powder chromatography and fractional crystallisation eleven products have been isolated and are listed in the first column of the Table.

* Part V, *J.*, 1957, 1423.

[1] Wieland and Wishart, *Ber.*, 1914, **47**, 2082.
[2] Stetten and Stetten, *J. Biol. Chem.*, 1946, **164**, 85.
[3] Anderson and Wallis, *J. Amer. Chem. Soc.*, 1948, **70**, 2931.
[4] Kuhn, Quadbeck, and Röhm, *Annalen*, 1949, **565**, 1.
[5] Angyal, Gilham, and Macdonald, *J.*, 1957, 1417.
[6] Angyal and McHugh, *Chem. and Ind.*, 1955, 947.
[7] Angyal, Gilham, and McHugh, *J.*, 1957, 1432.

Considerable loss of oxygen by hydrogenolysis had occurred and the products ranged from *cyclo*hexanetriols to inositols, the latter accounting for only 25—30% of the yield. The triols and tetrols—of which there are many possible isomers—were not separated and the bulk of these fractions failed to crystallise. Several quercitols were obtained but, undoubtedly, others remained in mother-liquors. However, the chromatographic behaviour

Products isolated from the hydrogenation of hexahydroxybenzene.

Compound	Yield (%) Pd, 20°, 1 atm.	Ni, 120—140°, 150 atm.	10% Pd–C, 20°, 1 atm.
Inositols :			
myo- (1235/46)	17·2	1·9	7·5
cis- (123456/)	1·7 *	4·7	20·0
scyllo- (135/246)	1·2	0·1	1·0
epi- (12345/6)	0·2	1·8	0·3
(±)- (124/356)	2·9	—	0·05
neo- (123/456)	—	0·05	—
allo- (1234/56)	—	0·1	—
*cis*Inososе	2·0	—	—
Quercitols :			
cis- (12345/)	2·7	8·1	0·4
epi- (1235/4)	0·5	1·9	—
scyllo- (135/24)	0·05	0·1	0·05
*cyclo*Hexanetetrol (acetate, m. p. 124°)	1·2	—	—
all-*cis*-*cyclo*Hexane-1 : 2 : 3-triol	—	0·5	—
Reducing compound (m. p. 160—161°)	0·3	—	—

* A yield of 4·5% was obtained in a run in which PtO_2 was used to reduce any inososes remaining after the Pd-catalysed hydrogenation.

of the inositols is well known [7] and it was therefore possible to isolate all those which were formed in the reaction; it is estimated that *allo*-, *muco*-, and *neo*-inositol—which were not obtained—could not have been present in more than 0·1% yield. Thus fractions which should have contained *allo*- and *muco*-inositol failed to show the Scherer reaction characteristic for inositols; and *neo*inositol would have been separated by virtue of its very low solubility (as it has been in the high-pressure run, see below). In accordance with the earlier reports, *myo*inositol was the main product of the reaction though in a yield much below that claimed by Wieland and Wishart.

Some of the fractions, when examined by paper chromatography in acetone–water (4 : 1) and phenol–water (4 : 1), appeared to contain *epi*inositol, but the acetate obtained from them by acetylation was not identical with *epi*inositol acetate, or with the acetate of any other known inositol. Further examination by paper chromatography showed that the new compound could be separated from *epi*inositol in butan-1-ol–acetic acid–water (4 : 1 : 1) and in ethyl acetate–acetic acid–water (3 : 1 : 1). It gave the Scherer test, and analyses of this compound and its derivatives confirmed that it was an inositol. Since all the other isomers predicted by theory are known, the new compound must have the all-*cis*-configuration (I) * and has been named *cis*inositol. It completes the stereoisomeric group of inositols and is of interest as the only known compound which has, in its stable chair conformation, three axial hydroxyl groups on the same side of the ring. The energy of interaction between these hydroxyl groups has been estimated at 5·7 kcal./mole.[8]

In its final stages the hydrogenation is very slow, and a paper chromatogram of the mixture, sprayed with a reagent which detects reducing compounds only,[9] showed a number of spots, indicating the presence of polyhydroxy-ketones. (The hydrogenation can be completed at this stage by the use of Adams catalyst.) One of these was isolated

* Hydroxyl groups are indicated but not shown in the formulæ.

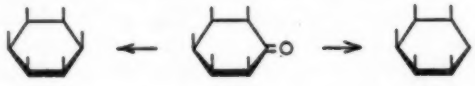
[8] Angyal and McHugh, *Chem. and Ind.*, 1956, 1147.

[9] Magasanik, Franzl, and Chargaff, *J. Amer. Chem. Soc.*, 1952, **74**, 2621.

during the chromatographic separation and was found to be a new inosose. On hydrogenation with platinum oxide in neutral solution it gave *cis*inositol, and reduction by sodium amalgam yielded *epi*inositol. The inosose therefore has the all-*cis*-configuration (II).

A new quercitol was isolated from the hydrogenation of tetrahydroxybenzoquinone; the same quercitol was also obtained by hydrogenation of *cis*inosose with a platinum catalyst in acid solution. This reaction, which is known [10] to remove the keto-group without affecting the hydroxyl groups, proves that the new quercitol has the all-*cis*-configuration (III) and hence it has been named *cis*quercitol.

Hydrogenation over Raney Nickel.—Successful separation of the cyclitols produced in the hydrogenation over palladium suggested that a re-investigation of the hydrogenation of tetrahydroxybenzoquinone over Raney nickel at high temperature and pressure, as described by Anderson and Wallis,[3] might establish the identity of their products. The reaction was carried out according to their description and the product was examined by paper chromatography. The pattern of the spots was different from that obtained on the hydrogenation over palladium, mainly in the region of the faster-running components; no reducing compounds were present. The mixture was again separated by cellulose-powder chromatography and by crystallisation of the cyclitols or their acetates; the ten products obtained are listed in the second column of the Table.



(I) (II) (III)

The total amount of inositols produced in this hydrogenation is much less (about 9%) than in the run with palladium and the yield of *myo*inositol is small. No pronounced stereospecificity is evident but the *cis*-isomer predominates amongst both the inositols and the quercitols.

Anderson and Wallis isolated five crystalline compounds considered to be inositols. Two were identified as *myo*- and *scyllo*-inositol, and another, m. p. 213—214°, was established as an inositol by analysis and Scherer test; its acetate was reported to melt at 205—206°. Since the acetate of *cis*inositol melts at 208°, it is probable that Anderson and Wallis had this compound in hand. *cis*Inositol itself melts at 377° (uncorr.) when placed on a preheated block but decomposes on slow heating; this decomposition may have been mistaken for melting by the American authors. No other compound isolated from the hydrogenation has an acetate melting near 205°.

The other two compounds, isolated as their acetates by Anderson and Wallis, were regarded as inositols although their analyses were closer to those of quercitol acetates and their behaviour in the Scherer test was not reported. One acetate, m. p. 189—190°, was tentatively identified as *epi*inositol acetate (m. p. 188°) and this identification was probably correct, although *scyllo*quercitol acetate (m. p. 193°) cannot be excluded. The second acetate, m. p. 139—140°, was—in view of the products obtained by us—probably not that of an inositol, but rather *epi*quercitol acetate (m. p. 140°); *allo*inositol acetate (m. p. 144°) appears less likely since it is present in such small amount in the hydrogenation mixture.

The Stereochemistry of the Hydrogenation.—Full knowledge of the products of the hydrogenation does not explain the surprising predominance of *myo*inositol. Even more surprising—in view of the large number of possible isomers—is the recent report [11] that hydrogenation of 1 : 4-diaminotetrahydroxybenzene and of triaminophloroglucinol produces mainly a single isomer in each case (in 43 and 60% yield, respectively); explanation of this stereospecificity will have to await the determination of the configuration of the products.

[10] Posternak, *Helv. Chim. Acta*, 1941, **24**, 1045.
[11] Quadbeck and Röhm, *Chem. Ber.*, 1956, **89**, 1645.

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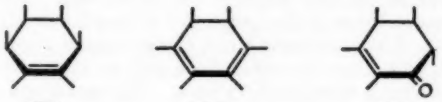
The formation of *cis*inositol and *cis*inosose is readily explained: if a molecule of hexahydroxybenzene takes up three molecules of hydrogen while adsorbed on the catalyst surface, *cis*inositol will result in view of the known *cis*-addition of hydrogen over metallic catalysts. If only two mols. of hydrogen are taken up, the resulting enediol (IV) can isomerise to *cis*inosose (II) which gives *cis*inositol on further hydrogenation.

The formation of *myo*inositol, on the other hand, is not readily explained. It is not formed from *cis*inositol by the epimerisation which is known to occur [12] with some *cyclo*hexanols in the presence of metallic catalysts: prolonged shaking of *cis*inositol with palladium does not cause detectable isomerisation. The *trans*-arrangement of some hydroxyl groups in *myo*inositol must be the result of isomerisation at intermediate stages of the hydrogenation.

Desorption from the catalyst surface after the uptake of only one mol. of hydrogen gives a dihydrobenzene derivative (V) which can react in several ways: (i) It can aromatise by the loss of water to give pentahydroxybenzene. This explains the formation of quercitols and, by repetition of the process, *cyclo*hexanetetrols, etc. (ii) It can be re-adsorbed on the catalyst and further hydrogenated. (iii) It can rearrange to an unsaturated ketone (VI) with formation of a new asymmetric centre. Further hydrogenation will yield an enediol which can also ketonise. It is possible that, as the result of



(IV) (V) (VI)

these reversible keto–enol interconversions, the thermodynamically most stable inosose, the all-equatorial *scyllo*inosose, could emerge as the main product. The hydrogenation of *scyllo*inosose is known [10] to yield *myo*inositol accompanied by small amounts of *scyllo*inositol. *scyllo*Inosose has not been isolated from the hydrogenation mixture but a compound of its R_P value has been detected on paper chromatograms. *cis*Inosose, once formed, is not isomerised when shaken with the catalyst.

It was found that, in accordance with the report by Anderson and Wallis, neither hexaacetoxybenzene nor hexamethoxybenzene could be reduced over the palladium catalyst at atmospheric pressure. This may indicate that hexahydroxybenzene is hydrogenated *via* a tautomeric form; mechanisms based on this assumption, however, fail to explain the formation of *myo*inositol.

It appears therefore that complete hydrogenation of hexahydroxybenzene while adsorbed on the catalyst yields *cis*inositol, whereas desorption after the uptake of one mol. of hydrogen will result in hydrogenolysis and also in the formation of *myo*inositol. It is concluded that prolongation of the contact with the catalyst, by augmenting its surface, would increase the yield of *cis*inositol. The palladium catalyst prepared according to Kuhn *et al.* appears to have a small surface: it coagulates readily and does not yield a fine suspension. A catalyst of presumably larger surface was prepared by precipitating palladium, according to the method of Kuhn *et al.*, but in the presence of activated charcoal. Hydrogenation with this palladium–carbon catalyst, at room temperature and atmospheric pressure, did not proceed faster than with palladium alone but the proportion of the products, listed in the third column of the Table, was different. The yield of inositols was somewhat higher and *cis*-, not *myo*-, inositol was the main product. The use of high pressure in the hydrogenation over palladium–carbon did not further increase the yield of *cis*inositol.

By use of the palladium–carbon catalyst, the interesting *cis*inositol can be produced in reasonable yield but its separation from other cyclitols by chromatography is tedious. Its

[12] Wicker, *J.*, 1956, 2165.

strong ability to form a complex with boric acid [13] suggested another method of separation: it was found that *cis*inositol was completely removed from aqueous solution by the borate form of a strongly basic anion-exchange resin.[14] Some other cyclitols, however, also reacted with the resin and were only slowly removed from it by water; complete separation of *cis*inositol by this method alone was not achieved. A new quercitol of unknown configuration was separated in small amounts from the resin.

Experimental

M. p.s are corrected. Paper chromatography was carried out as previously described; [7] R_P values refer to acetone–water (4 : 1 v/v) unless otherwise stated. Cyclitols were identified by mixed m. p.s and by paper chromatography in at least two solvent systems. Acetyl derivatives were prepared by 30 minutes' heating, on the steam-bath, with acetic anhydride and sulphuric acid (19 : 1 v/v); the mixture was poured into water, any solid which separated after 1—2 hr. was filtered off, and the rest of the acetate was recovered by extraction with chloroform.

Chromatography on Cellulose Powder.—Acetone–water (4 : 1 v/v) was used as the mobile phase unless otherwise stated. Compounds emerged from the cellulose-powder column [5] generally in order of decreasing R_P values, but one exception wa noted. (±)-Inositol (R_P 0·27) was not eluted ahead of *cis*- and *epi*-inositol (R_P of both 0·22s); in every case *cis*- and *epi*-inositol appeared first, and the (±)-isomer emerged around the middle of the (*cis* + *epi*)-fraction but disappeared before that fraction was completely eluted. This phenomenon is explained by the difference between the properties of powdered cellulose and cellulose filter paper.[15] It was also found that *cis*inositol was eluted from the column somewhat ahead of the *epi*-isomer (though they have the same R_P value) so that *cis*inositol crystallised from earlier fractions and *epi*inositol from the later ones. The separation was not complete, however, and a mixture of the two inositols was left in the mother-liquors.

Palladium Catalyst.—A solution of palladium chloride (1·7 g.) in water (400 ml.) and 10N-hydrochloric acid (10 ml.) was neutralised at 80° with 25% sodium hydroxide, and then formic acid (0·5 ml.) was added. The evolution of carbon dioxide, as described by Kuhn *et al.*,[4] could not be seen at this point, so additional 25% sodium hydroxide (7·5 ml.) and formic acid (1·0 ml.) were added as soon as a brown cloudiness developed in the solution. The precipitated catalyst was washed with hot water until the washings were no longer alkaline, and dried over sulphuric acid.

The 10% palladium–carbon catalyst was prepared in the same way except that unwashed activated charcoal (10 g.) was suspended in the solution with vigorous stirring. Additional sodium hydroxide and formic acid were added one minute after the first addition of formic acid. The use of acid-washed charcoal seems to lower the activity of the catalyst.

It has been reported, both by Wieland and Wishart [1] and by Kuhn *et al.*,[4] that traces of hydrogen chloride inactivated their palladium catalyst. Since the catalyst is prepared under alkaline conditions this may be taken as an indication that traces of absorbed alkali are responsible for the activity of the catalyst. It was found, however, that addition of small amounts of hydrochloric acid to the hydrogenation mixture made no difference to the rate of the hydrogenation with either the palladium or the palladium–carbon catalyst; it even caused a slight increase with the former. The 10% palladised charcoal catalyst prepared, in a solution of sodium acetate, according to Mozingo [16] also produced inositols, as shown by paper chromatography, though hydrogenation was very slow.

Hydrogenation of Tetrahydroxybenzoquinone with Palladium Catalyst.—Hexahydroxybenzene is only slightly soluble in water and is precipitated during the hydrogenation, covering the catalyst. It was therefore advisable to carry out this first stage of the hydrogenation by the use of a small amount of palladised charcoal [16] (which is more effective in this step) and add the palladium catalyst subsequently.

A suspension of tetrahydroxybenzoquinone [17] (4 g.) and 10% palladised charcoal [16] (0·2 g.) in water (250 ml.) was hydrogenated at room temperature and pressure. The initial reduction

[13] Angyal and McHugh, *J.*, 1957, 1423.
[14] Lock and Richards, *J.*, 1955, 3024.
[15] Balston and Talbot, "Guide to Filter Paper and Cellulose Powder Chromatography," Reeve, Angel and Balston, London, 1952, p. 16.
[16] Mozingo, *Org. Synth.*, Coll. Vol. III, p. 685.
[17] Priesler and Berger, *J. Amer. Chem. Soc.*, 1942, **64**, 67.

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to hexahydroxybenzene was complete in 7 hr., whereupon palladium catalyst (1·0 g.) was added and the hydrogenation continued. More catalyst (total, 3 g.) was added whenever the uptake of hydrogen became slow; after the last addition, only 30 ml. of hydrogen were absorbed. The reduction took 82 hr. and 2280 ml. of hydrogen (calc. 2210 ml.) were taken up. The catalyst was removed and washed with hot water, and the filtrate was evaporated under reduced pressure and dried over sulphuric acid.

scyllo*Inositol*. The partly crystalline residue (3·14 g.) was warmed with water (6 ml.) and filtered; the solid, recrystallised from water–ethanol, had m. p. 330—340° (47 mg.). Acetylation and recrystallisation from ethanol gave hexa-acetyl*scyllo*inositol, m. p. 292—293°, mixed m. p. 293—295°.

The filtrate after isolation of *scyllo*inositol was seeded with *neo*inositol and left at 0° overnight but no further crystallisation took place. The solution was diluted with acetone and run through a column of cellulose powder (12 × 1¼″ containing about 150 g. of cellulose): 250 fractions of 10 ml. were collected and examined by paper chromatography. Fractions 44—75 contained a mixture of inositols, and fractions 76—250 contained *myo*inositol; their isolation is described further below.

cis*Inosose*. Fractions 20—36 contained a reducing compound, as shown by paper chromatography and development with ferricyanide–ferric chloride.[9] They were combined, concentrated to 5 ml., and treated with phenylhydrazine according to the method of Carter *et al.*;[18] cooling and scratching gave red crystals which were recrystallised from methanol–water, to yield cis*inosose phenylhydrazone* (120 mg.); a further crystallisation gave colourless crystals, decomp. 150—160° (Found: N, 10·35. $C_{12}H_{16}O_5N_2$ requires N, 10·45%).

The phenylhydrazone (90 mg.) was reconverted into the inosose by the method of Carter *et al.*;[18] recrystallisation from water–ethanol gave cis*inosose* (44 mg.), m. p. 179—180° (decomp.) (Found: C, 40·15; H, 5·65. $C_6H_{10}O_6$ requires C, 40·45; H, 5·65%).

The mother-liquors from the separation of the phenylhydrazone were freed from phenylhydrazine by warming with benzaldehyde and extraction with ether; they were then evaporated and the residue chromatographed through the cellulose column. Fractions 1—20 and 37—43 of the original separation were combined in such a way that each combination gave only two or three spots on paper chromatograms; these combinations were then also run separately through the column. In this manner the components of each mixture were separated; corresponding fractions of each chromatogram were combined with each other to give seven fractions (A—G), each showing a single black spot on a silver nitrate-developed paper chromatogram. Each fraction was evaporated to a small volume, treated with charcoal, dissolved in the minimum amount of ethanol or aqueous ethanol, and stored at 0°. If no crystallisation occurred after several weeks, the solution was evaporated, the residue being acetylated and stored under the minimum amount of ethanol.

Fraction A, R_F 0·85 (the R_F values of the fractions are only approximate) (73 mg.). After acetylation, crystals of a cyclo*hexanetetrol tetra-acetate* (40 mg.) slowly separated. Recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) they had m. p. 124° (Found: C, 53·45; H, 6·5. $C_{14}H_{20}O_8$ requires C, 53·15; H, 6·35%). Deacetylation with boiling ethanol containing 5% of hydrochloric acid gave crystals which darkened at 195—200° and melted at 205—210°. The residue from the mother-liquors of the acetate was distilled under reduced pressure to give a mixture of *cyclo*hexanetetrol tetra-acetates which did not crystallise (Found: C, 53·7; H, 6·4%).

Fraction B, R_F 0·70 (60 mg.). No crystalline material could be isolated. In another run (from 10 g. of tetrahydroxybenzoquinone) this fraction showed strong reducing properties and, after further chromatography, crystals (44 mg.) were obtained. Recrystallisation from ethanol gave a product (26 mg.), m. p. 160—161°, which reduced Fehling's solution in the cold and so probably contained a keto-group. It was acetylated but then failed to crystallise.

Fractions C, D, and E [R_F 0·62 (75 mg.), 0·53 (115 mg.), *and* 0·45 (135 mg.), *respectively*]. No crystalline product could be obtained. After acetylation, each fraction was distilled under reduced pressure and analysed: the first two proved to be mixtures of tetra-acetoxy*cyclo*hexanes and the last a mixture of penta-*O*-acetylquercitols (Found: Fraction C: C, 52·55; H, 6·4. Fraction D: C, 52·9; H, 6·4. Calc. for $C_{14}H_{20}O_8$: C, 53·15; H, 6·35%. Fraction E: Found: C, 51·55; H, 5·85. Calc. for $C_{16}H_{22}O_{10}$: C, 51·35; H, 5·9%).

cis- *and* epi-*Quercitol*. From Fraction F (R_F 0·39, 200 mg.) crystals (105 mg.) separated.

[18] Carter, Belinskey, Clark, Flynn, Lythe, McCasland, and Robbins, *J. Biol. Chem.*, 1948, **174**, 422.

Acetylation and crystallisation from ethanol–water gave *penta*-O-*acetyl*cis*quercitol*, m. p. 162·5° (Found: C, 51·6; H, 5·95. $C_{16}H_{22}O_{10}$ requires C, 51·35; H, 5·9%). A sublimed sample had m. p. 165·5°. Hydrolysis of the acetate, followed by sublimation *in vacuo*, gave crystals of cis*quercitol*, m. p. 235—240° (decomp.) (Found: C, 44·05; H, 7·5. $C_6H_{12}O_5$ requires C, 43·9; H, 7·35%).

The mother-liquors of the *cis*quercitol fraction, after several weeks, yielded a further crop of crystals (18 mg.). Recrystallisation from water–ethanol gave *epi*quercitol, m. p. 206—209° (decomp.), mixed m. p. 207—209° (decomp.). Acetylation yielded penta-*O*-acetyl*epi*quercitol, m. p. and mixed m. p. 141—142°.

scyllo*Quercitol*. From Fraction G (R_F 0·31, 165 mg.) a few crystals separated. Acetylation, followed by sublimation *in vacuo*, gave *scyllo*quercitol acetate, m. p. and mixed m. p. 193—194°. The acetate was hydrolysed to the quercitol, m. p. 235°, mixed m. p. 236°. The mother-liquors of this fraction gave no Scherer test, indicating the absence of *allo*inositol (R_F 0·30).

(±)-, epi-, *and* cis-*Inositol*. Fractions 44—75 of the preliminary separation were found, by paper chromatography, to contain *cis*-, *epi*-, and (±)-inositol. Since the first two have the same R_F value in acetone–water, another solvent system was used for separation. The content of these fractions (390 mg.) was dissolved in butan-1-ol–acetic acid–water (4 : 1 : 1 v/v, 30 ml.); after 2 days, (±)-inositol (120 mg.) had separated. After two crystallisations from water–ethanol the product was acetylated, to yield the hexa-acetate, m. p. and mixed m. p. 110°.

The mother-liquors from the isolation of (±)-inositol were run through a cellulose-powder column (9 × 1½ in.) in butan-1-ol–acetic acid–water (4 : 1 : 1); separation of *cis*- and *epi*-inositol was not complete but from the appropriate fractions *cis*-inositol (70 mg.) was obtained by crystallisation from water–ethanol. Acetylation and crystallisation from ethanol–water gave cis*inositol hexa-acetate*, m. p. 208° (Found: C, 49·95; H, 5·45. $C_{18}H_{24}O_{12}$ requires C, 50·0; H, 5·6%). Hydrolysis with boiling ethanol containing 5% of hydrogen chloride gave cis*inositol* which was crystallised from water–ethanol (Found: C, 40·3; H, 6·9. $C_6H_{12}O_6$ requires C, 40·0; H, 6·7%). *cis*Inositol decomposes on slow heating but its uncorrected m. p. was found to be 377° (decomp.) by placing samples on a preheated aluminium block; the corrected m. p. would be approx. 390°. The *hexabenzoate*, prepared by the method described for (±)-inositol by Fletcher and Findlay,[19] crystallised from anhydrous ethanol and melted at 252° (Found: C, 71·85; H, 4·55. $C_{48}H_{36}O_{12}$ requires C, 71·65; H, 4·5%).

The fractions containing mainly *epi*inositol were combined and evaporated, and the residue was acetylated. From a solution in aqueous ethanol, *epi*inositol acetate (11 mg.) slowly crystallised; after sublimation *in vacuo* it melted at 187° (mixed m. p. 187—188°).

myo*Inositol*. Fractions 76—250 of the preliminary separation were evaporated to give *myo*inositol (712 mg.); after one crystallisation from aqueous ethanol its m. p. was 222—224°.

Hydrogenation of cis*Inosose*.—*cis*Inosose (18 mg.) was hydrogenated for 3 hr. in N-hydrochloric acid with Adams catalyst (5 mg.). After removal of the platinum, the solution was evaporated in a desiccator over sodium hydroxide, and the residue was separated by chromatography on a small cellulose-powder column. The inositol fraction (3 mg.) was acetylated, and the product, recrystallised from ethanol–water, had m. p. 207—208°, undepressed by admixture of *cis*inositol acetate. The quercitol fraction was acetylated to give *cis*-quercitol penta-acetate (5 mg.), m. p. 162—163°, undepressed by a sample obtained from the hydrogenation of tetrahydroxybenzoquinone.

After a small-scale hydrogenation in water with Adams catalyst paper chromatography in butan-1-ol–acetic acid–water showed the formation of *cis*inositol accompanied by a trace of *epi*inositol.

Reduction of cis*Inosose with Sodium Amalgam*.—To a solution of *cis*inosose (50 mg.) in water (3 ml.), kept slightly acid by additions of N-sulphuric acid as required, sodium amalgam (1 g.) was added in several portions with shaking. When the solution no longer reduced Fehling solution, it was evaporated; acetylation of the residue gave penta-*O*-acetyl*epi*inositol which, after crystallisation from ethanol–water, had m. p. and mixed m. p. 188°.

Hydrogenation of Tetrahydroxybenzoquinone with Raney Nickel.—A mixture of tetrahydroxybenzoquinone (10 g.), Raney nickel W-2[20] (2 teaspoons; *ca.* 6 g.), ethanol (100 ml.), and water (70 ml.) was hydrogenated in a steel autoclave at 120°/150 atm. for 40 min. and then at 140° for 30 min. The solution was filtered, concentrated under reduced pressure, and dried over sulphuric acid.

[19] Fletcher and Findlay, *J. Amer. Chem. Soc.*, 1948, **70**, 4051.
[20] Mozingo, *Org. Synth.*, Coll. Vol. III, p. 181.

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scyllo- *and* neo-*Inositol.* The syrupy residue (7·4 g.) was diluted with methanol and crystals (65 mg.) gradually separated. Crystallisation from water–ethanol gave a product (37 mg.), m. p. >280°; on addition of more ethanol, the mother-liquor deposited further crystals (11 mg.), m. p. 218—220°, identified as *myo*inositol. The former product was acetylated and the resulting mixture of acetates was separated by extraction with hot ethanol. The ethanol solution deposited *neo*inositol hexa-acetate (8 mg.), m. p. 254°, mixed m. p. with a pure sample (m. p. 257°) 256°. The ethanol-insoluble residue (32 mg.) was sublimed *in vacuo* to give *scyllo*inositol hexa-acetate, m. p. 295—297°, mixed m. p. with an authentic sample (m. p. 292—294°) 293—295°.

The filtrate from the *scyllo*- and *neo*-inositol was worked up by cellulose-powder chromatography as described above. After preliminary separation all the fractions—except those containing *epi*-, *cis*-, and *myo*-inositol—were rechromatographed and the products grouped into Fractions A—F (not necessarily identical with the fractions carrying the same designations in the previous run). There was some overlapping of fractions: only those which appeared to show a single spot on the chromatogram were worked up.

Fraction A (R_F 0·77, 700 mg.) deposited crystals (125 mg.) contaminated by oil, when stored in ethanol–ethyl acetate at 0°. Recrystallisation to constant m. p. from ethanol–ethyl acetate gave all-*cis*-*cyclo*hexane-1:2:3-triol[21] (39 mg.), m. p. and mixed m. p. 146—147° (Found: C, 54·6; H, 9·1. Calc. for $C_6H_{12}O_3$: C, 54·55; H, 9·15%). The hexabenzoate had m.p. and mixed m. p. 145°.

Fractions B (R_F 0·61) and D (R_F 0·44) gave no crystalline products.

Fraction C (R_F 0·55, 300 mg.). Crystals (110 mg.), contaminated by oil, gradually separated. Fractional crystallisation gave three fractions: m. p. 220—235° (6 mg.), 165—170° (40 mg.), and 159—172° (8 mg.). Fractional sublimation *in vacuo* gave fractions of m. p. 135—145°, 177—187°, 197—225°, and 225—227°. No pure substance was obtained from this fraction.

cis*Quercitol.* Fraction E (R_F 0·39, 850 mg.) deposited crystals (770 mg.) from water–ethanol; recrystallisation gave *cis*quercitol (670 mg.), m. p. 235—240° (decomp.); its acetate had m. p. and mixed m. p. 163°. The mother-liquors gave no Scherer test, showing the absence of *muco*inositol.

epi- *and* scyllo-*Quercitol and* allo*Inositol.* Fraction F (R_F 0·33, 435 mg.) deposited crystals (180 mg.), m. p. 194—195°; several crystallisations gave *epi*quercitol (90 mg.), m. p. and mixed m. p. 208°. Acetylation gave a product which, after one crystallisation from ethanol–water, melted at 122—123° but after another crystallisation had m. p. 140°. *epi*Quercitol acetate was reported[22] to be dimorphous with m. p.s 123—124° and 142—143°.

The mother-liquors from *epi*quercitol—which gave the Scherer test, indicating the presence of *allo*inositol—were evaporated to dryness and chromatographed on a small cellulose-powder column. The fractions showing the presence of *allo*inositol contained a glass (80 mg.) which was acetylated and crystallised from ethanol–water. The first crystals (25 mg.), m. p. 188—191°, were recrystallised, to give *scyllo*quercitol acetate, m. p. and mixed m. p. 192—193°. Deacetylation yielded *scyllo*quercitol, m. p. and mixed m. p. 232°. The mother-liquors were concentrated, seeded with *allo*inositol acetate, and kept at 0°: crystals (29 mg.) slowly separated and, after one recrystallisation, had m. p. 136—139°. The substance was fractionally sublimed *in vacuo* and the last fraction, m. p. 142°, depressed the m. p. of *epi*quercitol acetate but not that of *allo*inositol acetate (m. p. 144°).

cis- *and* epi-*Inositol.* Fractions 51—70 of the preliminary separation, which contained *epi*- and *cis*-inositol, were evaporated to dryness; the residual syrup (510 mg.), on being dissolved in water–ethanol, deposited *epi*inositol (145 mg.; acetate, m. p. 186—187°). After concentration, more *epi*inositol (30 mg.; acetate, m. p. 187—188°) separated. Further concentration and inoculation caused the crystallisation of *cis*inositol (125 mg.; acetate, m. p. 205—206°).

Fractions 38—50 of the preliminary separation, which contained quercitols besides *epi*- and *cis*-inositol, were rechromatographed and the residue of the fractions containing only inositols (400 mg.) was crystallised from water–ethanol. The separated crystals (320 mg.) yielded *cis*-inositol (210 mg.; acetate, m. p. 206—207°) on recrystallisation.

All the mother-liquors of fractions 38—70 were combined and again run through the cellulose-powder column. The resulting fractions yielded (*a*) crystals (10 mg.), m. p. 183—190°, which were shown to be a mixture of *scyllo*- and *epi*-quercitol, (*b*) crude *cis*inositol (50 mg.;

[21] Lindemann and de Lange, *Annalen*, 1930, **483**, 31; Posternak and Ravenna, *Helv. Chim. Acta*, 1947, **30**, 441.

[22] May and Mosettig, *J. Org. Chem.*, 1949, **14**, 1137.

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acetate, m. p. 198—203°), and (*c*) crude *epi*inositol (16 mg.; acetate, m. p. 165—172°). There was no evidence from paper chromatography for the presence of (±)-inositol in any fraction.

myo*Inositol*. Fractions 76—100 of the preliminary separation gave *myo*inositol (190 mg.) on evaporation. After one crystallisation it melted at 222°.

Hydrogenation of Tetrahydroxybenzoquinone with Palladium–Carbon.—A suspension of the quinone (10 g.) and of palladium–carbon (1 g.) in water (200 ml.) was hydrogenated at room temperature and pressure. In one hr. 0·9 mol. of hydrogen was taken up (hexahydroxybenzene crystallised) and 1·0 mol. was reached after 5 hr. Further amounts of catalyst (a total of 10 g.) were added until the rate of hydrogen uptake became negligible (110 hr.). At an intermediate stage, paper chromatography showed the presence of *cis*inosose but at the end of the reaction no reducing substance was present. The catalyst was removed and washed with aqueous ethanol; paper chromatography of the filtrate showed a high concentration of *myo*- and *cis*-inositol and weaker spots at R_F 0·31 and 0·38. Evaporation under reduced pressure gave a resin (7·7 g.) which was taken up in methanol. *scyllo*Inositol (75 mg.) gradually crystallised; it was shown to be free from *neo*inositol by paper chromatography in phenol–water (4 : 1 w/w).

The solution decanted from the crystals was evaporated to dryness, the residue dissolved in water (7 ml.) and diluted with acetone (28 ml.); cellulose powder was added to absorb the precipitated oil. This mixture was then placed on top of the cellulose column and chromatographed as described above.

cis*Quercitol*. The contents of fractions 21—50 were run through the column again and the fractions containing *cis*-quercitol were evaporated; the residue (120 mg.) gave *cis*quercitol (40 mg.) on crystallisation from water–ethanol. The acetate had m. p. 162°, mixed m. p. 163°.

cis- *and* (±)-*Inositol*. Nearly all the *cis*inositol was in fractions 51—150; their semi-crystalline residue (3·9 g.) deposited *cis*inositol from water–ethanol, which was chromatographically pure after one recrystallisation (1·24 g.).

The mother-liquors were rechromatographed through the cellulose column, and the effluent was divided into three fractions. The first contained mainly *cis*inositol which crystallised from water–ethanol as needles (415 mg.). The mother-liquors yielded crystals (12 mg.), shown by chromatography to be those of (±)-inositol; its acetate had m. p. 105—107°. The second fraction slowly deposited crystals which were fractionally crystallised to yield pure *cis*inositol (440 mg.; acetate, m. p. 205—206°) and a mixture (160 mg.) of *cis*- and *epi*-inositol. The third fraction contained mainly *myo*inositol which was obtained pure (m. p. 224°, 420 mg.) by one crystallisation from water-ethanol.

scyllo*Quercitol and* epi*inositol*. All the mother-liquors and solid material remaining after the isolation of *cis*- and *myo*-inositol were combined and run through a cellulose column. The first product to emerge was acetylated and crystallised from ethanol, to yield *scyllo*quercitol acetate (10 mg.), m. p. and mixed m. p. 192°. The second half of the fractions containing *cis*- and *epi*-inositol was evaporated, and the residue acetylated, and crystallised from ethanol–water, to give *epi*inositol acetate (65 mg.), m. p. and mixed m. p. 187—188°. Considerable amount of *cis*inositol was still left in mother-liquors.

scyllo- *and* myo-*Inositol*. The contents (570 mg.) of fractions 181—260 were fractionally crystallised from water–ethanol: *scyllo*inositol (24 mg.) separated first. The remainder was combined with fractions 151—180, to yield *myo*inositol (360 mg.), m. p. 221—222°.

Hydrogenation of Tetrahydroxybenzoquinone with Palladium–Carbon at High Pressure.—The quinone (10 g.) in water (150 ml.) was hydrogenated with palladium–carbon for 2 hr.: 1·1 l. of hydrogen were absorbed and hexahydroxybenzene was precipitated. The mixture was transferred to a steel autoclave, more catalyst (10 g.) and water (100 ml.) were added, and the suspension was stirred under a hydrogen pressure of 100 atm. After 23 hr. the reduction was still incomplete; the mixture was further hydrogenated at 45—50° for 19 hr. after which no reducing compounds were present. The catalyst was removed and the filtrate was evaporated to dryness. The crude material (8·4 g.) was redissolved in a little water, leaving *scyllo*inositol (250 mg.) undissolved.

Absorption on ion-exchange resin. The filtrate was diluted to 300 ml. with water and was shaken for 20 min. with a strong base anion-exchange resin (Deacidite FF; 200 g.), converted into the borate form according to the directions of Lock and Richards.[14] Paper chromatography of the solution showed that all *cis*inositol had been removed but some *myo*- and *scyllo*-inositol and unidentified material remained. The solution was filtered; the filtrate (containing 1·8 g. of material) was not worked up.

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To remove the weakly bound cyclitols, the resin was shaken with water (300 ml.) for 1 hr.; the filtrate contained *myo*inositol. This process was repeated twenty times but even in the last washing *myo*inositol could still be detected. The combined washings were evaporated and the residue was repeatedly distilled with methanol until no more methyl borate was formed. The residue (1·3 g.) was found, by paper chromatography, to consist mainly of *myo*inositol but to contain another compound having R_P 0·44. To isolate the latter the residue was chromatographed on a cellulose column; the fractions showing a spot at R_P 0·44 gave a gum (135 mg.) on evaporation which, after acetylation, deposited crystals (50 mg.) from ethanol–water. Several recrystallisations gave a *quercitol penta-acetate*, m. p. 115—117° (Found: C, 51·5; H, 6·0. $C_{16}H_{22}O_{10}$ requires C, 51·35; H, 5·9%). After deacetylation, the quercitol decomposed at 230—240° without melting. It is not identical with any of the known quercitols.

Desorption from the resin. The resin was shaken twice with N-hydrochloric acid (400 ml.); the filtrates were evaporated, and boric acid was removed by distillation with methanol. Crystallisation from water–ethanol gave, first, *scyllo*inositol (55 mg.), then a crop of *cis*inositol (850 mg.). The mother-liquors were found to contain *cis*- and *epi*(or *scyllo*)-quercitol, *cis*-, *epi*-, and *myo*-inositol. By cellulose-powder chromatography *cis*quercitol (460 mg.) and *cis*inositol (340 mg.) were isolated; other fractions and mother-liquors, which contained more *cis*inositol, were not worked up.

The authors are indebted to Dr. E. Challen, of this School, and to Dr. W. Zimmerman, Microanalytical Laboratory, C.S.I.R.O., Melbourne, for the microanalyses.

School of Chemistry,
N.S.W. University of Technology, Sydney. [*Received, January 14th*, 1957.]

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728. *Cyclitols. Part VII.* Anhydroinositols and the "Epoxide Migration."*

By S. J. Angyal and P. T. Gilham.

Several 1 : 2-anhydroinositols have been prepared by the action of strong bases on appropriate toluene-*p*-sulphonyl compounds. In those anhydrides which have a hydroxyl group adjacent and *trans* to the epoxide ring, the epoxide is opened in alkaline solution by the hydroxyl group's attacking from the rear with the formation of a new epoxide ring ("epoxide migration"). The position of the equilibrium between two anhydroinositols has been established and has been shown to be governed by steric interactions.

The configuration of conduritol oxide has been determined.

A proposal is made for specifying the configuration of asymmetric cyclitols by a modified use of the sequence rule.

The Specification of Asymmetric Configuration in Cyclitols.—Several different proposals have recently been made [1,2,3] for logical naming and numbering of cyclitols; in consequence the nomenclature of cyclitols is in a confused state. It was hoped that a body of authority would put forward official proposals, but this hope has, so far, not materialised; in the meanwhile each proposed nomenclature is in limited use.

Whereas the method of nomenclature [2] employed in this Series of papers is unambiguous in its numbering and naming, it does not yet provide for the distinction between enantiomers (other than by structural formulæ). Rules to cover this point were submitted in Part I [2] but were withheld at the Editor's request. In the present paper it is necessary to specify the configuration of asymmetric cyclitols. The other proposed nomenclatures [1,3] provide such methods, but their adoption involves the fundamental objection

* Part VI, preceding paper.

[1] Fletcher, Anderson, and Lardy, *J. Org. Chem.*, 1951, **18**, 1238.
[2] Angyal, Macdonald, and Matheson, *J.*, 1952, 686.
[3] MacCasland, pamphlet available from Chemical Abstracts, Ohio State University, Columbus 10, Ohio.

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that their use of *D* and *L* depends on the method of enumeration employed and would necessitate altering the names and numbering used in this Series. Our original, unpublished, proposals do not now appear to offer any advantage.

A method of specifying configurations independent of a numbering system is provided by the "sequence rule." Its recent modification,[4] in contrast to its original form,[5] can deal with cyclitols; but its application to this field is cumbersome, requiring specification of the configuration of every carbon atom, and it completely obscures the *cis–trans*-relation of substituent groups which is the salient feature of cyclitol chemistry. Nevertheless, the sequence rule has the advantage that its specification of asymmetric configuration is independent of any other convention, such as numbering rules.

In the hope that international agreement on cyclitol nomenclature will eventually be reached, any method now advocated is regarded as temporary and should therefore introduce the minimum of new rules or conventions. It is now proposed, after discussion with the Editor, to use the modified sequence rule to distinguish between enantiomers, in a simplified way, namely, by specifying the configuration of only *one* carbon atom with its aid. By using the nomenclature proposed in Part I, *i.e.*, trivial prefixes as used in carbohydrate chemistry, only *one* specification is required to distinguish between enantiomers and therefore to describe the configuration of an asymmetric cyclitol fully.

In Part I [2] we proposed two rules for the numbering of cyclitols, *viz.*: (i) that the larger number of functional groups on one side of the hexagon be described by the lowest possible numbers; and (ii) if the hydrogen atom of a hydroxyl group is replaced by another group and if rule (i) has not by itself determined the numbering of this derivative unequivocally, then this substituted position shall be given the lowest number which remains available. It is now further proposed that the configuration of the *lowest numbered asymmetric carbon atom* (not always $C_{(1)}$) be specified by the modified sequence rule [4] as *R* or *S*. The label shall be written in parentheses preceded by the number of the carbon atom thus labelled, *e.g.*, (1*R*)-inositol; it is not strictly necessary to use this number but we propose to print it for clarity, in accordance with the proposals of Cahn, Ingold, and Prelog.[4]

This application of the sequence rule in the cyclitol series is very simple. Essentially, it requires the four groups attached to the carbon atom to be arranged in a priority sequence; if that sequence for the assemblage Cabcd is a,b,c,d, then it will be denoted as *R* if the sequence a→b→c traces a right-handed turn when viewed from a point on the side remote from d. (The sequence can be conveniently visualised by the use of an imaginary steering wheel.[4]) The opposite arrangement is denoted as *S*.

The priority sequence is, in the first instance, decided by the rule that higher atomic number precedes the lower. In most cases in cyclitol chemistry, oxygen will have the highest and hydrogen the lowest priority; the priority between the two carbons in the ring is determined by the atomic numbers of the atoms attached to them, or, if this fails, to the next atoms, etc. If this procedure fails to establish priority—as in the case of an unsubstituted inositol—it is decided by the rule that *cis* precedes *trans*.

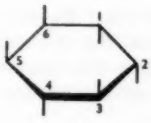
By this method, (+)-inositol (I) * becomes (1*S*)-inositol, the common natural quercitol, (+)-*proto*quercitol (II), is written as (1*R*)-*proto*quercitol, and (+)-bornesitol [6] (III) is named as (1*R*)-1-*O*-methyl*myo*inositol. Other examples appear in this paper.

"*Epoxide Migration.*"—Sugar epoxides (1 : 2-anhydro-sugars) have been extensively used as intermediates in carbohydrate chemistry: opening of the epoxide ring, which always occurs with inversion, yields epimeric sugars and their derivatives.[7] The method is of obvious use in cyclitol chemistry but until recently only one anhydroinositol had been

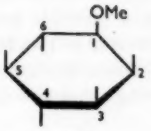
* Hydroxyl groups are indicated by their bonds, but not shown, in formulæ.

[4] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[5] Cahn, and Ingold, *J.*, 1951, 612.
[6] Angyal and Pitman, unpublished work.
[7] Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37.

reported, that made by epoxidation [8] of conduritol, a naturally occurring *cyclo*hexene-tetrol.[9] The configuration of this anhydroinositol has not been determined and it has not been used for the synthesis of other cyclitol derivatives. Recently, in Part III of this series,[10] two anhydroinositols were described and their cleavage utilised to prepare a new inositol and a new inositol methyl ether. The present paper extends this work, making


(I)

(II)



(III)

five of the possible ten 1 : 2-anhydroinositols known; work is in progress on two other anhydrides. No 1 : 3- or 1 : 4-anhydroinositol has yet been described.

The anhydroinositols were prepared in the usual way,[7] by treatment of *trans*-1 : 2-diol monotoluene-*p*-sulphonates with alkali. The epoxide ring is readily opened by nucleophilic reagents; thus alkalis give inositols, sodium methoxide gives inositol methyl ethers, ammonia gives inosamines,[11] etc.

In nucleophilic opening, the group which cleaves the epoxide ring may be within the molecule itself; for example, a suitably placed hydroxyl group, in the presence of bases, may attack the epoxide giving a cyclic ether. The best known example of this reaction is the rearrangement of scopine to scopoline.[12] In carbohydrate chemistry there are several known cases of 1 : 4-anhydride formation from epoxides.[7]

A hydroxyl group on a carbon atom adjacent to an epoxide ring could also carry out the intramolecular nucleophilic displacement: in this case the epoxide ring would open with the formation of another epoxide ring. This phenomenon will be referred to as " epoxide migration : "

Such a reaction was first postulated by Lake and Peat [13] to explain the formation of two epoxides, instead of the expected one, on treatment of methyl 2-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside with sodium methoxide. Buchanan [14] recorded another, similar case. Newth [15] recently assumed the occurrence of epoxide migration when he found that 1 : 6-anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose gave, not the expected 1 : 6-2 : 3-dianhydro-β-D-mannose, but 1 : 6-3 : 4-dianhydro-β-D-altrose; he gave a detailed discussion of the reaction. In these cases the epoxide migration was merely postulated; the actual conversion of one epoxide into another has, to our knowledge, not yet been described. The study of anhydroinositols has now enabled us to observe epoxide migration by converting one epoxide into another which was itself isolated, and by studying the position of the equilibrium.

On theoretical grounds the following predictions can be made concerning the occurrence of epoxide migration :

(i) Since the opening of an epoxide ring is a nucleophilic displacement on carbon,

[8] Schöpf and Arnold, *Annalen*, 1947, **558**, 123.
[9] Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756.
[10] Angyal and Matheson, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.
[11] Anderson, Abs. Papers, 130th Meeting, Amer. Chem. Soc., p. 27D; Allen, *J. Amer. Chem. Soc.*, 1957, **79**, 1167.
[12] Willstätter and Berner, *Ber.*, 1923, **56**, 1079.
[13] Lake and Peat, *J.*, 1939, 1069.
[14] Buchanan, *Chem. and Ind.*, 1954, 1484.
[15] Newth, *J.*, 1956, 441.

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occurring with inversion,[16] the entering group must attack the carbon from the side opposite to that of the epoxide-oxygen atom. In a *cyclo*hexane system the hydroxyl group should be *trans* and capable of taking up an axial position.

(ii) The hydroxyl group must be present as an anion; therefore, epoxide migration can occur only in the presence of strong bases.

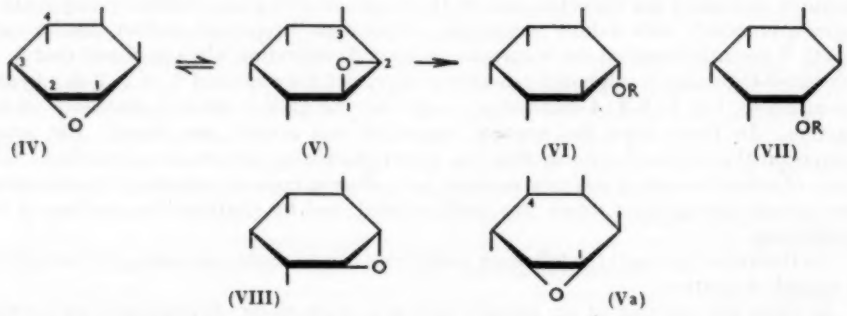
(iii) After migration, the new hydroxyl group will be *trans*-situated in respect of the new epoxide, in a suitable position for nucleophilic attack. Epoxide migration must therefore be a reversible reaction. The equivalence of starting and end product requires that the oxygen anion leaving the transition state, as well as the one entering it, be in an axial position; ring inversion thus occurs when the molecule passes through the transition state.

(iv) The position of the equilibrium will depend on the free energies of the two epoxides, the more stable one (as a rule, the isomer containing fewer axial substituents [17]) predominating.

The epoxide migrations observed amongst anhydroinositols, and also the cases described by Lake and Peat [13] and by Newth,[15] conform to the above rules.

Anhydroinositols.—Epoxide migration was first studied in the case of (1*S*)-1 : 2-anhydro-*allo*inositol (IV), prepared by mild acid hydrolysis of its di*iso*propylidene derivative.[10] Cleavage of the epoxide ring by dilute sulphuric acid gave the expected mixture of nearly equal quantities of *neo*- and (−)-inositol. Cleavage with hot alkali, however, gave a mixture of *myo*- (VI; R = H) and *allo*-inositol (VII; R = H), suggesting that migration had occurred before opening of the epoxide ring. Proof of this rearrangement was obtained by treating the anhydride (IV) with dilute barium hydroxide solution at room temperature: from this reaction a new anhydroinositol was isolated. This anhydride was cleaved by both acid and alkali to a mixture of *myo*- and *allo*-inositol, a reaction which restricts the structure of the anhydride to either (V) or (VIII), or their enantiomers.

Opening of the epoxide ring of the new anhydride with sodium methoxide provided an unequivocal answer to its structure because in this reaction a methoxyl group labels the carbon on which ring-opening had occurred. Two methyl ethers were isolated from this reaction: one, which was optically active, gave *allo*inositol on demethylation, and the other, a *meso*-compound, was identified as sequoyitol, 5-*O*-methyl*myo*inositol [18] (VI; R = Me). The latter can be formed only from (V) or from its enantiomer (by attack of a

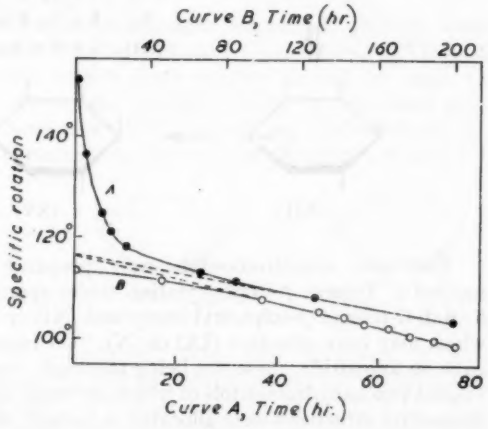


methoxide ion at $C_{(2)}$); structure (VIII), on the other hand, would give 4-*O*-methyl*myo*-inositol. The rearranged anhydride therefore has structure (V) or its enantiomer; the former, but not the latter, can be obtained from (IV) by epoxide migration. It is concluded

[16] Cf., *e.g.*, Winstein and Henderson in Elderfield's "Heterocyclic Compounds," J. Wiley and Sons, Inc., New York, 1950, Vol. I, p. 27.
[17] Cf., *e.g.*, Klyne, "Progress in Stereochemistry," Butterworths Ltd., London, 1954, Vol. I, p. 43.
[18] Anderson, Deluca, Bieder, and Post, *J. Amer. Chem. Soc.*, 1957, **79**, 1171.

therefore that (1*S*)-1 : 2-anhydro*allo*inositol (IV) underwent epoxide migration in alkaline medium to give (1*S*)-1 : 2-anhydro*neo*inositol (V), in accordance with the rules formulated above. The other methyl ether resulting from attack of methoxide ion on (V)—at $C_{(1)}$—must therefore be (1*S*)-1-*O*-methyl*allo*inositol (VII; R = Me); this conclusion has been confirmed by the synthesis of its enantiomer by an independent method.[19]

The epoxide migration can readily be followed polarimetrically since the anhydroinositols (IV) and (V) have specific rotations of +153° and +113°, respectively. The rotation does not come to a constant value, however, because of the simultaneous, though much slower, cleavage of the anhydrides; after a prolonged period in alkaline solution, only inositols were present. The rate of this hydrolysis is so slow that it can be considered as constant over the period of epoxide migration and extrapolation of the straight part of the curve (see Figure) to cut the *y* axis gives the final value for the epoxide migration, approx. +117°. This is higher than the rotation of anhydro*neo*inositol, suggesting an



Equilibration of anhydroinositols.

A, (1*S*)-1 : 2-Anhydro*allo*inositol (0·2583 g.) in 0·05N-barium hydroxide (10 ml.) at 20°. *B*, (1*S*)-1 : 2-Anhydro*neo*inositol (0·0925 g.) in 0·05N-barium hydroxide (10 ml.) at 20°.

equilibrium of the two anhydrides. The equilibrium was approached also from the other side (see Figure) and extrapolation * agrees with the value of approx. +117°. (The two curves are shown on the same Figure though the time-scales are different.) The value +117° shows that there are approximately 90% of anhydro*neo*- and 10% of anhydro*allo*-inositol in equilibrium at 20°. The equilibrium constant, *K*, is ~9 and calculation by the equation $\Delta F = -RT \ln K$ shows that anhydro*neo*inositol is more stable than its isomer by 1·3 kcal./mole.

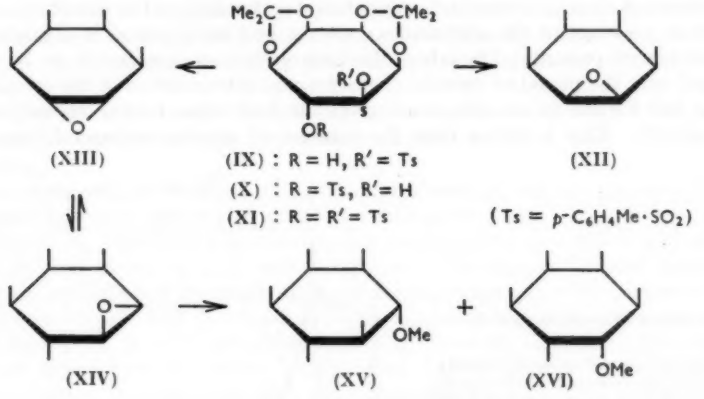
Writing the anhydro*neo*inositol as (V*a*) shows that it is an epimer of anhydro*allo*inositol (IV), differing only in the configuration at $C_{(4)}$. The latter compound has two, the former only one, axial hydroxyl group in its preferred conformation; hence the former is more stable. Winstein and Holness [20] gave the energy difference between an equatorial and an axial hydroxyl group, when isolated from other groups, as 0·8 kcal./mole; in our case the energy difference is greater because the axial hydroxyl group which is present in (IV), but not in (V), would suffer steric interaction from the oxygen atom of the epoxide ring.

It is seen that epoxide migration occurs under surprisingly mild conditions, namely, in dilute aqueous alkali solution at room temperature; these conditions are milder than those used for the cleavage of epoxides by bases. The rearrangement of scopine to scopoline (1 : 2-anhydride to 1 : 4-anhydride) is slower.[12] Since the usual conditions for preparing

* Although extrapolation of curve *A* is from two experimental points only, that of curve B is accurate and it is satisfactory that curve *A* fits this more precise determination.

[19] Angyal and Gilham, unpublished work.
[20] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

epoxides from bromohydrins or toluene-*p*-sulphonyl compounds are more vigorous than those required for migration, the initially formed (but less stable) epoxide is not usually obtained in those cases where epoxide migration can occur. In our example the less stable isomer was obtained because epoxide formation was carried out while the neighbouring hydroxyl groups were blocked by *iso*propylidene groups, and these were eventually removed under acidic conditions.



Two new anhydroinositols were prepared from 1 : 2-3 : 4-di-*O*-*iso*propylidene*epi*-inositol.[2] Toluene-*p*-sulphonylation, under appropriate conditions, readily gave either the 5 : 6-di-*O*-toluene-*p*-sulphonyl compound (XI) or a mono-*O*-toluene-*p*-sulphonyl derivative which may have structure (IX) or (X). On treatment with sodium methoxide each ester gave an anhydride, these not being identical; removal of the *iso*propylidene groups then yielded two anhydroinositols of which one must have structure (XII) and the other (XIII). Respective structures were allocated as a result of the study of the epoxide migration.

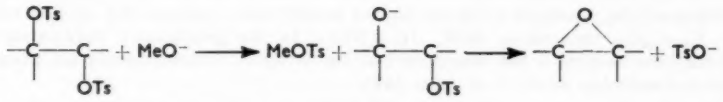
The anhydride made from the monotoluene-*p*-sulphonyl compound gave *epi*inositol on acid hydrolysis but *myo*- and *allo*-inositol on treatment with alkali; epoxide migration had therefore occurred. The rearranged anhydride was not isolated but its structure was established by cleavage with sodium methoxide which gave methyl ethers of *myo*inositol and of *allo*inositol. The former was shown to be (±)-4-*O*-methyl*myo*inositol (XV); although this racemic compound was previously unknown, its structural identity with ononitol,[21] the naturally occurring (+)-4-*O*-methyl*myo*inositol, was shown by the identity of the infrared spectra of their penta-acetates.[22] Formation of the ether (XV) and of a methyl ether of *allo*inositol proves that the rearranged anhydride is 1 : 2-anhydro*epi*inositol (XIV), and the methyl ether of *allo*inositol is consequently (±)-5-*O*-methyl*allo*inositol (XVI). (All the compounds formed from *epi*inositol are, of course, racemic and the formulæ show only one, arbitrarily chosen, enantiomer.) It follows that the original anhydride is (±)-5 : 6-anhydro*allo*inositol (XIII) and the parent monotoluene-*p*-sulphonyl ester is (±)-1 : 2-3 : 4-di-*O*-*iso*propylidene-5-*O*-toluene-*p*-sulphonyl*epi*inositol (IX).

The anhydride formed from the ditoluenesulphonyl derivative (XI) must therefore be 1 : 2-anhydro*cis*inositol (XII). It is hydrolysed by both acid and alkali to *epi*inositol; thus epoxide migration does not occur in this compound in which the hydroxyl groups are *cis* to the epoxide ring, although it contains two axial hydroxyl groups.

In the toluenesulphonylation of 1 : 2-3 : 4-di*iso*propylidene*epi*inositol the sulphonyl group would, of course, react preferentially with the less hindered oxygen atom. The

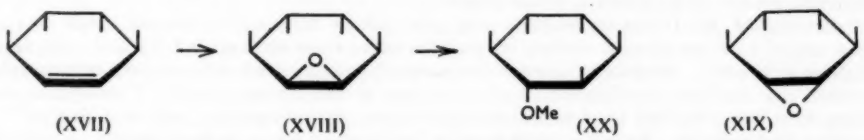
[21] Plouvier, *Compt. rend.*, 1955, **241**, 983.
[22] Angyal, Gilham, and Macdonald, *J.*, 1956, 1417.

planar formula may suggest that $O_{(5)}$—*cis* to the two *iso*propylidene groups—is hindered but inspection of an atomic model (Courtauld's) shows that both free hydroxyl groups are unhindered. The experimental evidence now indicates that, in fact, $O_{(5)}$ is more accessible than $O_{(6)}$. The direction of epoxide formation from disulphonyl compounds [10] such as (XI) has not been discussed previously. It appears probable that the first sulphonyl group is removed by O–S fission,[23] facilitated by the inductive effect of the other sulphonyloxy-group :



The more accessible sulphonyl group would be removed first, in our case the one on $O_{(5)}$, explaining the formation of the *cis*-anhydride (XII).

The reaction of the naturally occurring *cyclo*hexenetetrol, conduritol [9] (XVII), with perbenzoic acid gives only one epoxide,[8] which may be 2 : 3-anhydro*allo*inositol (XVIII) or 1 : 2-anhydro*muco*inositol (XIX). Opening with sodium methoxide can be used to distinguish between these possibilities : the former (XVIII) would be converted into 3-*O*-methyl-(±)-inositol (XX), whereas structure (XIX) would give 2-*O*-methyl-(±)-inositol without epoxide migration, or 1-*O*-methyl-(±)-inositol and *O*-methyl*scyllo*inositol



(XVII) (XVIII) (XX) (XIX)

if migration occurred. Only 3-*O*-methyl-(±)-inositol (XX) was obtained; it was identified by comparison with a sample made by mixing natural pinitol and its synthetic enantiomer.[24] Conduritol oxide is therefore 2 : 3-anhydro*allo*inositol (XVIII). The direction of epoxidation is in accordance with Henbest and Wilson's recent conclusion [25] that peracids will add oxygen to the double bond of allylic *cyclo*hexenols so as to produce an epoxide in *cis*-relation to the adjacent free hydroxyl group.

Schöpf and Schmetterling [26] prepared 2 : 3-epoxysuccindialdehyde from conduritol oxide by glycol fission with lead tetra-acetate. Any of the other 1 : 2-anhydroinositols would serve as a starting material, and the ready availability of 1 : 2-anhydro*allo*inositol will make this interesting dialdehyde more accessible.

Experimental

M. p.s are corrected.

(1S)-1 : 2-*Anhydro*allo*inositol* (IV).—(1*S*)-1 : 2-Anhydro-3 : 4-5 : 6-di-*O*-*iso*propylidene*allo*-inositol [10] (10 g.) was heated in acetic acid (20 ml.) and water (20 ml.) for ½ hr. on a steam-bath. After cooling, the product which crystallised was filtered off and washed with ethanol. Recrystallisation from aqueous ethanol gave the *anhydride* (4·05 g., 60%) as plates, $[\alpha]_D^{25}$ +153° (*c* 0·5 in H_2O) (Found : C, 44·15; H, 6·15. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). When heated to *ca.* 200°, the compound melts and sets to a hard glass, probably owing to polymerisation. Acid hydrolysis, as shown by paper chromatography,[27] yields (−)- and *neo*-inositol.

[23] Honeyman and Morgan, *J.*, 1955, **3664**; for discussion and references see Cope and Shen, *J. Amer. Chem. Soc.*, 1956, **78**, 5912.
[24] Angyal, Macdonald, and Matheson, *J.*, 1953, 3321.
[25] Henbest and Wilson, *Chem. and Ind.*, 1956, 659.
[26] Schöpf and Schmetterling, *Angew. Chem.*, 1952, **64**, 591.
[27] Angyal, Gilham, and McHugh, *J.*, 1956, 1432.

Alkaline Hydrolysis of (1S)-1 : 2-*Anhydro*allo*inositol*.—The anhydride (0·2 g.), dissolved in 0·5N-barium hydroxide (10 ml.), was set aside overnight and then heated on the steam-bath for 3 hr. After removal of the barium as carbonate, the solution was evaporated to dryness *in vacuo* and the residue was chromatographed on a cellulose-powder column [22] with acetone–water (4 : 1 v/v); 5 ml. fractions were collected. Fractions 10—18, which showed the presence of *allo*inositol by paper chromatography, were combined and evaporated to dryness; the gummy residue was acetylated by hot acetic anhydride–pyridine (1 : 1). Evaporation to dryness *in vacuo* and crystallisation from water gave *hexa*-O-*acetyl*allo*inositol* (101 mg.), m. p. 144°, undepressed by a sample prepared by the acetylation of *allo*inositol (Found : C, 50·05; H, 5·45. $C_{18}H_{24}O_{12}$ requires C, 50·0; H, 5·6%). In the preliminary publication on *allo*inositol [9] the hexa-acetate is not described but Dr. H. O. L. Fischer kindly informed us that Dr. Dangschat recorded its m. p. as 141—142°.

Fractions 30—44, on evaporation and acetylation, gave hexa-*O*-acetyl*myo*inositol (45 mg.), m. p. and mixed m. p. 210° (Found : C, 49·85; H, 5·55. Calc. for $C_{18}H_{24}O_{12}$: C, 50·0; H, 5·6%).

(1S)-1 : 2-*Anhydro*neo*inositol* (V).—(1*S*)-1 : 2-Anhydro*allo*inositol (1 g.) was dissolved in 0·5N-barium hydroxide solution (20 ml.) and set aside for 5 hr. After removal of the barium as carbonate, the solution was evaporated to dryness *in vacuo* and the residue was extracted several times with cold anhydrous ethanol. The extracts were concentrated *in vacuo* and the resulting crystals were recrystallised several times from anhydrous ethanol to yield the *anhydride* (0·3 g., 30%), m. p. 154°, $[\alpha]_D^{25}$ +113° (*c* 1·0 in H_2O) (Found : C, 44·65; H, 6·25. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). It is difficult to obtain this anhydride pure because the starting material, present in equilibrium, is less soluble.

Reaction of (1S)-1 : 2-*Anhydro*allo*inositol with Sodium Methoxide*.—The anhydride (0·4 g.) was added to a solution of sodium methoxide made from sodium (0·2 g.) and anhydrous methanol (10 ml.). After 24 hr. most of the material had dissolved and paper chromatography showed that the anhydro*allo*inositol had rearranged to anhydro*neo*inositol. The solution was then heated under reflux for 5 hr., after which paper chromatography indicated that all the epoxide had reacted. After the addition of a few drops of water, carbon dioxide was passed through the solution which was then evaporated to dryness *in vacuo*. The residue was dissolved in water (1 ml.), and the solution diluted with acetone (4 ml.), filtered, and chromatographed through a cellulose-powder column with acetone–water (4 : 1 v/v). Paper chromatography of the fractions showed two compounds with slight over-lapping.

Fractions containing the first compound (R_F 0·41) were combined and evaporated. The gummy residue (179 mg.) was acetylated with acetic anhydride–pyridine (1 : 1) on the steam-bath for 1 hr. Evaporation *in vacuo*, followed by crystallisation from water, gave (1S)-*penta*-O-*acetyl*-1-O-*methyl*allo*inositol*, m. p. 145—146°, $[\alpha]_D^{19}$ +9° (*c* 0·7 in $CHCl_3$) (Found : C, 50·8; H, 5·9. $C_{17}H_{24}O_{11}$ requires C, 50·5; H, 6·0%). Deacetylation gave the methyl ether of *allo*inositol as a gum. Demethylation with hydriodic acid, followed by acetylation, gave hexa-*O*-acetyl*allo*inositol, m. p. 144°.

The fractions containing the second methyl ether (R_F 0·33) were combined and evaporated. The residue (150 mg.) on crystallisation from ethanol gave sequoyitol, m. p. and mixed m. p. 241—242° (Found : C, 43·25; H, 7·35. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·25%).

(±)-1 : 2-3 : 4-*Di*-O-iso*propylidene*-5 : 6-*ditoluene*-p-*sulphonyl*epi*inositol* (XI).—1 : 2-3 : 4-Di-*O-iso*propylidene*epi*inositol [2] (2·9 g.) and toluene-*p*-sulphonyl chloride (8·5 g.) were dissolved in anhydrous pyridine (30 ml.). After one week the mixture was diluted with water and the precipitated product was filtered off and washed with water. Crystallisation from ethanol gave the *ditoluene*-p-*sulphonyl derivative* (5·64 g., 89%), m. p. 208—209° (Found : C, 55·05; H, 5·7. $C_{26}H_{32}O_{10}S_2$ requires C, 54·95; H, 5·65%).

1 : 2-*Anhydro*-3 : 4-5 : 6-*di*-O-iso*propylidene*cis*inositol*.—The ditoluene-*p*-sulphonyl compound (XI) (2·0 g.) was added to anhydrous methanol (20 ml.) in which sodium (0·5 g.) had been dissolved. The mixture was heated under reflux for 5 hr., then chloroform (40 ml.) was added to the dark mixture. After being washed with water and dried (Na_2SO_4), the solution was evaporated to dryness. The crystalline residue was sublimed at 110°/1 mm. and the sublimate recrystallised from light petroleum to yield the *anhydride* (447 mg., 54%), m. p. 142—143° (Found : C, 59·7; H, 7·45. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%).

1 : 2-*Anhydro*cis*inositol* (XII).—The above compound lost its *iso*propylidene groups when heated in 50% acetic acid at 100° for 30 min. Evaporation *in vacuo* and crystallisation from

XUM

ethanol gave the *anhydride* as plates, m. p. 59—60° (Found: C, 44·5; H, 6·3. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). Hydrolysis by sulphuric acid or sodium hydroxide gave *epi*inositol as the sole product shown by paper chromatography.

(±)-6-O-*Acetyl*-1 : 2-3 : 4-*di*-O-iso*propylidene*-5-O-*toluene*-p-*sulphonyl*epi*inositol*.—1 : 2-3 : 4-Di-*O*-*iso*propylidene*epi*inositol [3] (1·0 g.) and toluene-*p*-sulphonyl chloride (0·72 g.) were dissolved in anhydrous pyridine (5 ml.). After one week, acetic anhydride (3 ml.) was added and the mixture kept for a further day. The solution was then poured on ice, and the precipitated gum (1·6 g.), which slowly solidified, was crystallised from methanol to give the *compound* as plates (1·0 g., 56%), m. p. 182° (Found: C, 54·9; H, 6·0. $C_{21}H_{28}O_9S$ requires C, 55·25; H, 6·2%).

Heating on the steam-bath with 2N-hydrochloric acid for 1 hr. and crystallisation from water gave (±)-5-O-*toluene*-p-*sulphonyl*epi*inositol*, m. p. 227° (decomp.) (Found: C, 46·6; H, 5·4. $C_{13}H_{18}O_8S$ requires C, 46·7; H, 5·45%).

5 : 6-*Anhydro*-1 : 2-3 : 4-*di*-O-iso*propylidene*allo*inositol*.—The above acetyl toluene-*p*-sulphonyl compound (1·0 g.) was added to anhydrous methanol (20 ml.) in which sodium (0·25 g.) had been dissolved. The mixture was warmed until the compound dissolved and then set aside for 24 hr. Chloroform was added, and the solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was extracted with light petroleum which, on concentration, deposited needles; crystallisation from light petroleum gave the *anhydride* (0·41 g., 78%), m. p. 97—98° (Found: C, 59·65; H, 7·4. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%).

5 : 6-*Anhydro*allo*inositol* (XIII).—The above compound (1·0 g.) was heated on the steam-bath in 50% acetic acid (4 ml.) for 1 hr. Evaporation *in vacuo* left a crystalline residue; it was extracted twice with ethyl acetate from which the *anhydride* (0·3 g., 45%), m. p. 120—122°, crystallised (Found: C, 44·45; H, 6·2. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). Another preparation gave a product melting at 148—150° which had the same R_P values. Paper chromatography after acid hydrolysis showed *epi*inositol and after alkaline hydrolysis *allo*- and *myo*-inositol.

Reaction of 5 : 6-*Anhydro*allo*inositol with Sodium Methoxide*.—The anhydride (0·2 g.) was added to a solution of sodium methoxide made from sodium (0·2 g.) and anhydrous methanol (15 ml.), and the solution was heated under reflux for 10 hr. After neutralisation with hydrochloric acid and evaporation, the residue was extracted with anhydrous methanol, and the contents of this solution were chromatographed through a cellulose-powder column with acetone–water (4 : 1 v/v).

The faster-moving material (210 mg.), which did not crystallise, was acetylated and crystallised from water to give (±)-5-O-*methyl*allo*inositol penta-acetate*, m. p. 124° (Found: C, 50·5; H, 5·95. $C_{17}H_{24}O_{11}$ requires C, 50·5; H, 6·0%).

The slower-moving material was acetylated and crystallised from ethanol–water to yield (±)-4-O-*methyl*myo*inositol penta-acetate* (8 mg.), m. p. 129—130° (Found: C, 50·6; H, 5·9%).

Reaction of Conduritol Oxide with Sodium Methoxide.—The oxide was prepared by Schöpf and Arnold's method [8] and melted, as described by them, at 112°. A later report [26] gives m. p. 130°. Crude oxide (made from 135 mg. of conduritol) was heated for 8 hr. with methanol (10 ml.) in which sodium (0·1 g.) had been dissolved. After treatment with carbon dioxide and evaporation, the residue was acetylated and crystallised from water to give the 3-O-*methyl*-(±)-*inositol penta-acetate* (40 mg.), m. p. 125° (Found: C, 50·65; H, 5·85%). For comparison, a sample was prepared by hydrolysing (1*R*)-3-*O*-methyl-1 : 2-5 : 6-di-*O*-*iso*propylideneinositol [24] with dilute acid, mixing the resulting (1*R*)-3-*O*-methylinositol with an equal amount of pinitol and acetylating the mixture. The penta-acetate (Found: C, 50·65; H, 6·0%) melted at 125° and did not depress the m. p. of the previous sample.

The authors thank Dr. Laurens Anderson (Madison) for the gift of conduritol, Dr. H. O. L. Fischer (Berkeley) for *allo*inositol, and Dr. E. Challen and Mr. D. G. Weeden for the microanalyses.

SCHOOL OF CHEMISTRY,
N.S.W. UNIVERSITY OF TECHNOLOGY, SYDNEY. [*Received, January 14th*, 1957.]

XUM

729. *The Kinetics of Ionic Polymerisation. Part VII.* The Polymerisation of Alkyl Vinyl Ethers with the Boron Trifluoride–Ether Complex.*

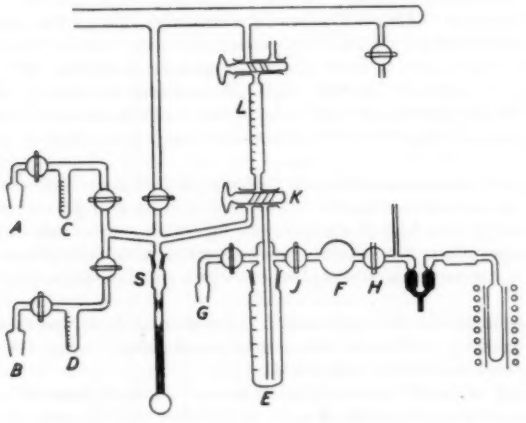
By J. D. Coombes and D. D. Eley.

In previous papers [1] the kinetics of the polymerisation of alkyl vinyl ethers with various catalysts were examined and a carbonium-ion mechanism was postulated. The present investigation is concerned with the polymerisation in solution of a pair of vinyl ethers catalysed by a stable co-ordination complex, boron trifluoride–diethyl ether.

Experimental

Reaction Velocity.—The technique used was similar to that of Eley and Richards,[1a] the polymerisations being followed in evacuated sealed dilatometers of 9 c.c. capacity and accurately known stem calibrations of approximately 0·05 c.c. per cm. Except for activation-

Fig. 1. *Vacuum apparatus for filling dilatometer.*



energy determinations all reactions were carried out at 25°. Solutions for rate determinations were prepared in an all-glass apparatus (Fig. 1) capable of being evacuated to 10^{-6} mm. Hg. Monomer and solvent were outgassed and stored over sodium in vessels attached to *A* and *B* respectively. Immediately before an experiment they were distilled *in vacuo* into the calibrated vessels *C* and *D* and the required volumes finally distilled into the dilatometer. This diluted solution of monomer was cooled and outgassed at least three times.

The catalyst solution was prepared in vessel *E*. Calcium fluoroborate, dried at 120° for 24 hr. *in vacuo*, was heated to 250° by means of a Nichrome-wound electric furnace. The boron trifluoride evolved by the high-temperature decomposition was passed over sodium fluoride, to remove hydrogen fluoride, and into a 100 c.c. calibrated volume *F*, the pressure in which could be measured with a mercury manometer. At a known pressure a sample was isolated by closing tap *H*, and condensed into *E* with liquid air.

Ethyl ether, outgassed and stored over sodium in a vessel attached to *G*, was condensed on the frozen boron trifluoride and the mixture allowed to warm slowly to room temperature. The volume of the solution was noted. This catalyst solution was outgassed at least three times. Portions were drawn up into the calibrated tube *L* and discharged into the dilatometer,

* Part VI, *J.*, 1954, 1677.

[1] (*a*) Eley and Richard, *Trans. Faraday Soc.*, 1949, **45**, 425, 436; (*b*) Eley and Saunders, *J.*, 1952, 4167; 1954, 1668, 1672, 1677.

containing frozen monomer solutions, *via* the two-way tap *K*. The frozen dilatometer was evacuated, sealed off, and stored at −180°. In the later experiments it was found possible to simplify this technique, allowing a transference of catalyst solution through the air without in any way altering the results obtained.

Densities (ρ) of monomer (M) and polymer (P) samples were determined at 25° so that initial rates of change of volume could be converted into reaction velocities in moles $l.^{-1}$ $min.^{-1}$. The average values used which agree with those of Eley and Saunders [1b] (*loc. cit.*) and others [2] were: *n*-butyl vinyl ether, $\rho_M = 0{\cdot}7733$ g./c.c., $\rho_P = 0{\cdot}9053$ g./c.c.; 2-chloroethyl vinyl ether, $\rho_M = 1{\cdot}039$ g./c.c., $\rho_P = 1{\cdot}234$ g./c.c.

The dilatometers were opened after 20%—30% polymerisation, the catalyst was destroyed by addition of a 5% solution of sodium hydroxide in water, and the polymer isolated according to the method of Eley and Richards.[1a]

Polymers.—All polymers isolated were transparent viscous liquids, those of *n*-butyl vinyl ether being colourless, and those of 2-chloroethyl vinyl ether pale yellow. Their molecular weights were determined by the Staudinger method. In each case the viscosity of a benzene solution was measured at five or six concentrations and the intrinsic viscosity (or limiting viscosity number) $[\eta]$ determined by extrapolation of the plot η_{sp}/c against c, which was linear in all cases. If c is in base moles per litre then it was found that (cf. Appendix)

$$[\eta] = 3{\cdot}8 \times 10^{-4}M$$

All polymer molecular weights in this paper were calculated from observed viscosity data through the above relation.

Materials.—Boron trifluoride. A high-purity sample, kindly given by the National Smelting Co. Ltd. (Avonmouth), was purified by Bistline's method.[3] The diethyl ether complex was purified by Laubengayer and Finlay's method to remove silicon tetrafluoride,[4] and mixed with calcium fluoride (B.D.H. " pure ") and kept for 24 hr. Excess of ether was removed by heating, the sample plugged with glass wool, and the glass vessel sealed to the vacuum apparatus.

Diethyl ether. The B.D.H. product, purified by Taylor and Smith's method,[5] was kept over sulphuric acid for 12 hr., washed, and mixed with saturated potassium permanganate solution containing 20 g. of sodium hydroxide. After standing for 24 hr. it was treated with water, concentrated sulphuric acid, and water again, and dried ($CaCl_2$). The product was distilled from sodium, the middle fraction being collected.

Vinyl ethers. The commercial products, purified by Schildknecht's method,[6] were washed five times with an equal volume of water made slightly alkaline with potassium hydroxide, dried (Na), and distilled *in vacuo*, the middle fraction being collected.

Ethylene dichloride. The commercial product was washed with 5% sodium hydroxide solution, then water, and distilled from phosphoric oxide, the middle fraction being collected.

Results

Reaction Velocity.—The reaction curves were linear up to 10% polymerisation and induction periods were normally absent. In some cases induction periods of a few minutes were found which are attributed to impurities.

The reaction velocity was examined as a function of monomer concentration [M], and catalyst concentration [C] for each monomer. At low monomer concentrations, the initial velocities v fit the equation:

$$v = -\mathrm{d}[\mathrm{M}]/\mathrm{d}t = k\,[\mathrm{M}]^2[\mathrm{C}] \quad \ldots\ldots\ldots \quad (1)$$

The results obtained are shown in Fig. 2 and give the overall rate constants, k : *n*-butyl vinyl ether, 16·5; 2-chloroethyl vinyl ether, 4·5 $l.^2$ $mole^{-2}$ $min.^{-1}$.

Overall Activation Energy.—A series of reaction rates were determined at five different temperatures in the range 20—40° with solutions containing constant amounts of monomer

[2] " Monomers," ed. Blout and Mark, Interscience, New York, 1951.
[3] Bistline, *Rev. Sci. Instr.*, 1948, **19**, 846.
[4] Laubengayer and Finlay, *J. Amer. Chem. Soc.*, 1943, **65**, 884.
[5] Taylor and Smith, *ibid.*, 1922, **44**, 2457.
[6] Schildknecht, in ref. 2.

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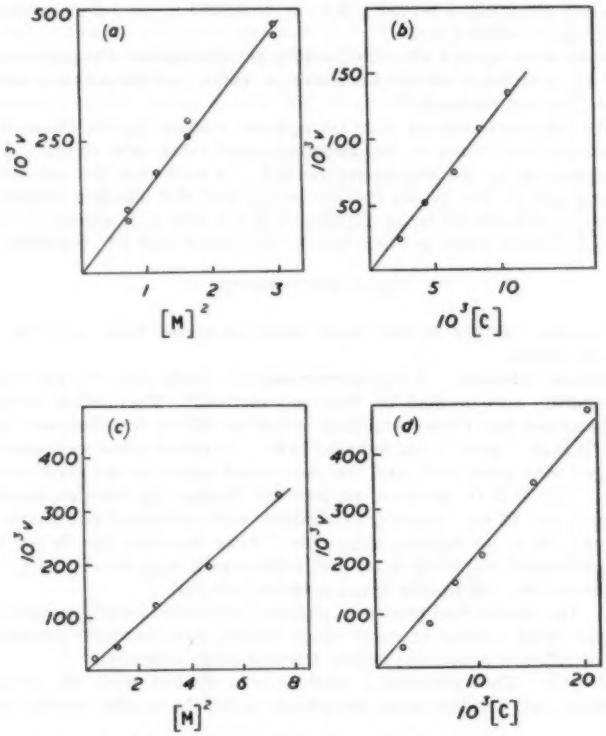
and catalyst. The results shown in Fig. 3 give the overall activation energies, E: *n*-butyl vinyl ether, 6·0 ± 0·5; 2-chloroethyl vinyl ether, E = 6·0 ± 0·2 kcal. mole^{-1}.

Molecular Weight of Poly-(n-butyl Vinyl Ether).—Two series of experiments were carried out at 25°. In one the monomer concentration was constant at 2·15 moles l.$^{-1}$ with varying

FIG. 2. *Order of the reaction.*



(*a*) Effect of [M] with *n*-butyl vinyl ether ([C] = 9·53mM).
(*b*) Effect of [C] with *n*-butyl vinyl ether ([M] = 0·859M).
(*c*) Effect of [M] with 2-chloroethyl vinyl ether ([C] = 10·1mM).
(*d*) Effect of [C] with 2-chloroethyl vinyl ether ([M] = 2·17M).

catalyst concentration; in the other the catalyst concentration was 10·2 mmoles l.$^{-1}$ with varying amounts of monomer. The results are shown in Table 1.

TABLE 1. *Molecular Weights.*

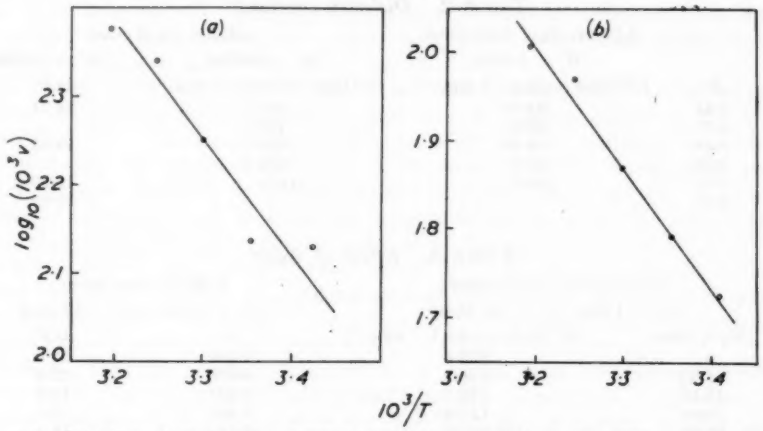
Varying catalyst, [M] = 2·15M.			Varying monomer [C] = 10·2mM.			Varying monomer [C] = 10·2mM.		
[C] (mM)	[η]	D.P.	[M] (M)	[η]	D.P.	[M] (M)	[η]	D.P.
5·1	1·250	32·9	1·29	0·895	23·6	3·01	1·868	49·2
10·2	1·250	32·9	1·72	1·249	32·0	3·44	1·953	51·4
15·3	1·180	31·0	2·15	1·565	41·2	3·87	2·000	52·6
20·4	1·115	29·3	2·58	1·720	45·3			
25·5	1·111	29·2						

The degree of polymerisation, D.P., is almost independent of [C], and linearly dependent on [M] at low values, reaching a maximum value as the monomer concentration [M] increases, as found earlier with stannic chloride and octyl vinyl ether.[1a]

A series of polymers were prepared in the temperature range 15—35° from a solution containing 2·15M-*n*-butyl vinyl ether and 9·35mM catalyst. The results obtained, shown in Fig. 4, give an " activation energy " $E_{D.P.} = -3{\cdot}0 \pm 0{\cdot}5$ kcal. mole^{-1}.

Dielectric Constant.—A series of molecular-weight and rate determinations were carried out on solutions containing fixed amounts of monomer and catalyst, but varying amounts of

FIG. 3. *Overall activation energy.*



(*a*) *n*-Butyl vinyl ether ([M] = 0·859M), (*b*) 2-chloroethyl vinyl ether ([M] = 1·084M).

FIG. 4. *The " activation energy " for D.P. for poly-*(n-*butyl vinyl ether*).

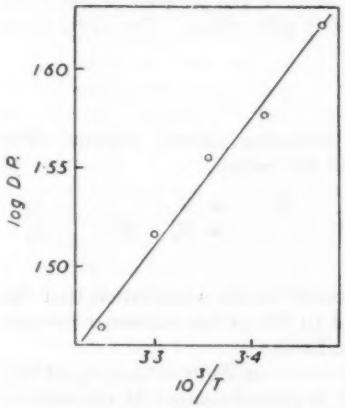
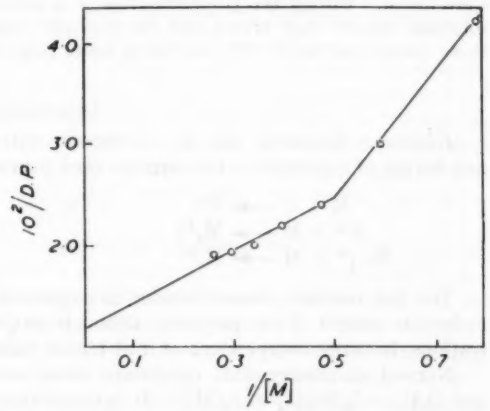


FIG. 5. *The effect of monomer concentration on D.P. of poly-*(n-*butyl vinyl ether*).



ethylene dichloride. Ethylene dichloride was chosen since it would not be expected to form a complex with boron trifluoride. Booth and Martin [7] found no evidence for compound formation between HCl and BF_3, and Booth and Frary [8] were unable to prepare a mixed boron trihalide. This is consistent with Meier's observation [9] that boron trifluoride in methyl chloride does not polymerise *n*-butene.

The results obtained at 25° are shown in Table 2.

[7] Booth and Martin, *J. Amer. Chem. Soc.*, 1942, **64**, 2198; *Chem. Rev.*, 1943, **33**, 57.
[8] Booth and Frary, *J. Amer. Chem. Soc.*, 1943, **65**, 1836.
[9] Meier, quoted by Plesch, *J. Appl. Chem.*, 1951, **1**, 269.

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The rates of both polymerisations increase exponentially with the dielectric constant of the solution, although the molecular weight is decreased. Eley and Richards [1a] found a similar rate increase for octyl vinyl ether.

Water.—The effect of water on the rate of polymerisation of a solution of 2-chloroethyl vinyl ether and the molecular weight of *n*-butyl vinyl ether polymers was examined. The results are shown in Table 3.

TABLE 2. *Dielectric constant.*

	2-Chloroethyl vinyl ether	*n*-Butyl vinyl ether	
	[M] = 1·084M	[M] = 0·859M	[M] = 1·289M
D	10^3 Rate (moles $l.^{-1}$ $min.^{-1}$)	10^3 Rate (moles $l.^{-1}$ $min.^{-1}$)	D.P.
4·34	34·99	195·1	26·71
4·70	59·00	439·0	—
5·08	78·62	609·0	15·95
5·50	100·9	794·3	—
5·92	140·3	1070	12·29
6·72	—	—	12·89

TABLE 3. *Effect of water.*

	2-Chloroethyl vinyl ether	*n*-Butyl vinyl ether	
	[M] = 1·08M; [C] = 25·58mM	[M] = 1·72M; [C] = 19·2mM	
$[H_2O]$ (mM)	10^3 Rate (moles $l.^{-1}$ $min.^{-1}$)	[η]	D.P.
0	133·4	1·250	32·9
8·33	126·3	0·890	23·4
16·66	139·7	0·621	16·3
25·00	125·3	0·485	12·8
33·33	131·0	0·418	11·0
41·66	—	0·361	9·5

Although the addition of water does not affect the rate, it causes marked induction periods which increased with increasing water concentration. Induction periods of up to 50 min. were found. During the polymerisation of *n*-butyl vinyl ether in the presence of water the solutions turned deep brown and the polymers isolated were pale yellow. The intensity of these colours increased with increasing water concentration.

DISCUSSION

Kinetics.—Equation (1) is consistent with the following kinetic scheme. The numbering of constants is the same as used previously in this Series.

$$\left.\begin{aligned} M + C &\longrightarrow M^* \\ M^* + M &\longrightarrow M_2^* \\ M_{n-1}^* + M &\longrightarrow M_n^* \end{aligned}\right\} \quad k_2, k_3 \qquad \begin{aligned} M_n^* &\longrightarrow M_n \quad k_4 \\ M_n^* + M &\longrightarrow M_n + M^* \quad k_5 \end{aligned}$$

The last reaction, chain transfer, is suggested to account for the observation that the molecular weight of the polymer, although proportional to [M] at low monomer concentrations, becomes independent of it at higher values (see Table 1).

Normal stationary-state conditions being assumed, $v = -d[M]/dt = (k_2k_3/k_4)[M]^2[C]$ and D.P. $= k_3[M]/(k_4 + k_5[M])$. It is found that if D.P. is plotted against [M] the relation is initially linear ($k_4 \gg k_5[M]$), giving a slope $k_3/k_4 = 18{\cdot}7$ l. $mole^{-1}$, and reaches a maximum where transfer becomes dominant ($k_5[M] \gg k_4$). This is clearly similar to the results found by Eley and Richards [1a] for stannic chloride. Alternatively, the equation may be put into the reciprocal form $1/\text{D.P.} = k_5/k_3 + k_4/(k_3[M])$.

In Fig. 5 1/D.P. is plotted against 1/[M] and it is seen that there is not a perfect fit to this relation. There is a discontinuity at low values of the monomer concentration (<2 M), which corresponds to a kind of threshold value which must be exceeded before transfer can set in. The reason for this behaviour is obscure, but it may be connected with the effects of traces of water in the solvents. Above this monomer concentration

there is a straight-line relation for 5 points, with a slope k_4/k_3 which is the reciprocal of the value 18·7 quoted above, and an intercept on the 1/D.P. axis which gives $k_5/k_3 = 1{\cdot}1 \times 10^{-2}$.

Activation Energies.—The overall activation energy, E, for the reaction has the same value, 6·0 kcal. mole^{-1}, for each monomer. Now $E = E_2 + E_3 - E_4$, where E_2, E_3, and E_4 are the activation energies associated with the individual steps; E_2 may or may not be composite. The molecular-weight "activation energy," $E_{D.P.}$, is equal to $E_3 - E_4$ and for *n*-butyl vinyl ether has the value $-3{\cdot}0$ kcal. mole^{-1}. Thus E_2 for *n*-butyl vinyl ether is equal to 9·0 kcal. mole^{-1}. The overall rate constant for this monomer, 16·5 l.^{2} mole^{-2} min.$^{-1}$, is equal to k_2k_3/k_4. Using the value of k_3/k_4, 18·7 l. mole^{-1}, from molecular-weight data above, we find that k_2 is 0·88 l. mole^{-1} min.$^{-1}$.

These values of the rate constant and the activation energy for the initiation provide an estimate of the entropy of activation equal to -35 ± 5 e.u. mole^{-1} in the standard state of 1 mole l.$^{-1}$. This high negative value must involve the creation of an ion-pair in solution and may be compared with the value found [10] for the Menschutkin reaction $Et_3N + EtBr \longrightarrow Et_4N^+Br^-$ in acetone–benzene of about -40 e.u. mole^{-1}.

A similar calculation can be made by using published data for the system stannic chloride–octyl vinyl ether–light petroleum.[1a] Here $k_2k_3/k_4 = 24$ l.^{2} mole^{-2} min.$^{-1}$ * and $k_3/k_4 = 117$ l. mole^{-1}, and the activation energy $E_2 = 13{,}300$ cal. Hence it may be calculated that $\Delta S_2^{\ddagger} = -27{\cdot}2$ e.u., suggesting that here also we are concerned with the creation of an ion-pair. In this case the ion-pair probably arises from the interaction of the stannic chloride with the vinyl ether monomer acting as cocatalyst.[11]

Initiation.—The absence of half-powers of [C] in the rate expression and the low dielectric constant of diethyl ether solvent (4·3) exclude the possibility of free ions' being the active species. The polar but un-ionised $BF_3{\cdot}OEt_2$ molecule, or the ion-pair $Et^+BF_3OEt^-$, must be considered as the effective initiator. The ion-pair $Et^+BF_3OEt^-$ is likely to be solvated to an oxonium compound $Et_3O^+BF_3{\cdot}OEt^-$, the solvation energy more than compensating for the small loss of Coulombic attraction energy attendant upon the greater charge separation involved.

A sample of ethoxonium fluoroborate, $Et_3O{\cdot}BF_4$, prepared by Meerwein's method [12] was found to polymerise a sample of *n*-butyl vinyl ether instantaneously.

Termination.—The anionic fragment $BF_3O{\cdot}Et^-$ cannot form a co-ordinate bond with the carbonium ion, and proton extraction from the latter must be the operative termination mechanism. This is confirmed by the observation that polymers prepared in the region where transfer was unimportant rapidly decolorised a solution of bromine in carbon tetrachloride. The polymer did not contain boron. Further evidence is provided by the observation that one catalyst molecule could initiate several polymer chains, again in a region where little transfer was occurring.

Dielectric Constant.—The results of Table 2 show that increasing the dielectric constant of the solution leads to a logarithmic increase in reaction rate, but a decrease in the molecular weight of the polymer formed. Eley and Richards [1a] found a similar increase in rate with no increase in molecular weight when investigating octyl vinyl ether.

In view of Overberger and Endres's observation [13] that it is the net electron-donating character of a transfer agent that determines its efficiency, it is unlikely that ethylene dichloride is acting in this capacity. It must be concluded that the decrease in molecular weight is a dielectric effect.

The ratio k_3/k_4, from the molecular-weight results, must be decreased at higher dielectric

* The third-order constants k quoted in Eley and Richards's [1a] paper, Table 1, p. 429; Fig. 5, p. 432; and p. 440 are in fact values of 10^4k. The necessity for this correction invalidates a remark by Eley made at the Dublin Symposium (*Sci. Proc. Roy. Dublin Soc.*, 1950, **25**, 137).

[10] Wynne-Jones and Eyring, *J. Chem. Phys.*, 1935, **3**, 492.
[11] Hamann, Plesch, and Skinner, *Sci. Proc. Roy. Dublin Soc.*, 1950, **25**, 131.
[12] Meerwein, *J. prakt. Chem.*, 1939, **154**, 83.
[13] Overberger and Endres, *J. Polymer Sci.*, 1955, **16**, 283.

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constant and this is doubtless due to an increase in k_4 since the reaction (proton extraction) involves a concentration of electrostatic charge. The overall rate constant k_2k_3/k_4 is increased however. Thus k_2, the initiation reaction, is the step most affected, as is to be expected since this is the only reaction involving the actual creation of charges in solution.

The initiation reaction would be expected to obey Kirkwood's equation.[14] Non-electrostatic forces being neglected,

$$\log k_2 = \log k_0 - \frac{1}{kT} \cdot \frac{D-1}{2D+1}\left[\frac{\mu_C^2}{r_C^3} + \frac{\mu_M^2}{r_M^3} - \frac{\mu^2}{r^3}\right]$$

where $k_0 = \alpha kTK_0^{\ddagger}/h$. Here $K_0^{\ddagger}$ is the equilibrium constant between the activated complex and the initial reactants, D is the dielectric constant, μ_C and μ_M are the dipole moments of catalyst and monomer respectively and μ that of the activated complex, and

FIG. 6. *The effect of solvent dielectric constant (Kirkwood theory) on the rate of polymerisation for (A) n-butyl vinyl ether and (B) 2-chloroethyl vinyl ether.*

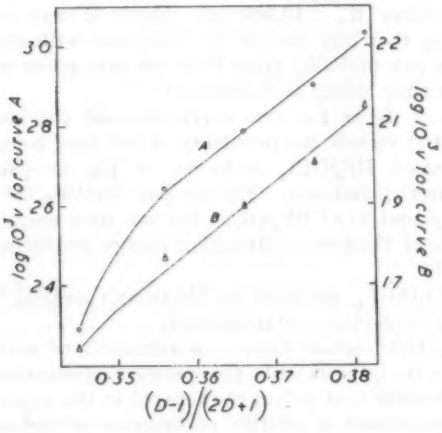
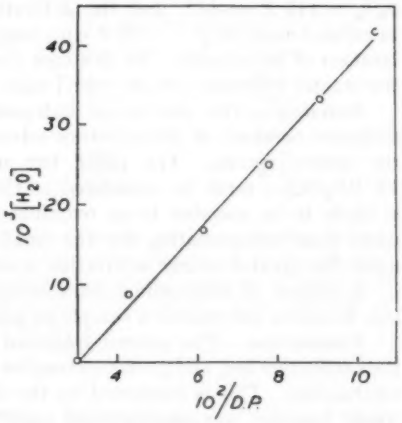


FIG. 7. *Effect of* $[H_2O]$ *on D.P. of poly-(n-butyl vinyl ether).*



r's similarly apply to the molecular radii. Thus a plot of log k_2 against $(D-1)/(2D+1)$ should be linear, with a slope of $-(1/kT)[(\mu_C^2/r_C^3) + (\mu_M^2/r_M^3) - (\mu^2/r^3)]$. Individual values of k_2 are not known, but since this is the reaction predominantly affected the error in using values of the overall rate constant $k = k_2k_3/k_4$ should not be prohibitive.

A plot of $\log_{10}k$ against $(D-1)/(2D+1)$ is shown for both monomers in Fig. 6. The slopes are equal and positive, showing that $\mu > (\mu_M + \mu_C)$, as is to be expected where the final products are ionised.

Effect of Water.—As seen from Table 3, water lowers the molecular weight of the polymer but does not affect the rate of the reaction. Quantitatively this molecular-weight lowering may be expressed by Mayo's chain-transfer equation:

$$1/(\text{D.P.})_n = 1/(\text{D.P.})_0 + (k_6/k_3)([\text{R}]/[\text{M}])$$

where we have a transfer step $\text{M}^* + \text{R} \longrightarrow \text{M} + \text{R}^*$ . . . . . k_6

Here D.P. is the molecular weight in presence of transfer agent, $(\text{D.P.})_0$ that in its absence, and [R] the concentration of transfer agent.

[14] Kirkwood, *J. Chem. Phys.*, 1934, **2**, 351.

A plot of 1/D.P. against $[H_2O]$ is shown in Fig. 7, giving a value $k_6/k_3 = 3{\cdot}1$.

Using the data of Eley and Richards [1a] and Eley and Pepper [16] we can calculate values of k_6/k_3 for other systems as follows:

Vinyl ether	Catalyst	Transfer Agent	k_6/k_3
n-Butyl	$SnCl_4$	BuOH	7·2
n-Butyl	$BF_3{\cdot}OEt_2$	H_2O	3·1
Octyl	I_2	BuOH	34·8

Butyl alcohol is a more efficient transfer agent than water, in accord with its greater electron availability. The anomalous value obtained with iodine as catalyst is probably due to the catalyst itself acting as a transfer agent. This is supported by the observation [1a] that iodine gave only low-molecular-weight polymers in contrast to those obtained with other catalysts.

Appendix

Viscosity Molecular Weights.—The molecular weights M were determined cryoscopically for 6 specimens of poly-(*n*-butyl vinyl ether). For each specimen a range of concentrations

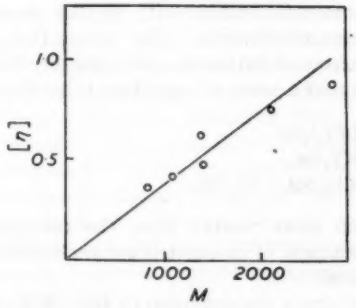


Fig. 8. *Relation between* $[\eta]$ *and cryoscopic molecular weight,* M.

in benzene was examined, and the molecular weights evaluated from the extrapolated values of $(\Delta/c)_{c\to 0}$, where Δ is the depression and c the concentration. The limiting viscosity number $[\eta]$ was determined with an Ostwald viscometer. The results are shown in Fig. 8., from which is derived the Staudinger relation $[\eta] = 3{\cdot}8 \times 10^{-4}M$ when c is in base moles per litre.

It is noted that the range of M taken is only 832 to 2702 while in the kinetic work the method was used for polymers up to $M = 5260$ (D.P. = 52·6). However, the earlier results of Eley and Richards [1a] support the validity of the relation to $M = 5000$ for poly-(2-ethylhexyl vinyl ether) where a Staudinger constant of $5{\cdot}0 \times 10^{-4}$ was found for light petroleum (b. p. 60—68°) as solvent.

The authors thank the National Smelting Co. Ltd. (Avonmouth) for a gift of boron trifluoride, and the Trustees of Courtaulds Scientific and Educational Trust Fund for a scholarship (to J. D. C.).

The University, Nottingham. [*Received, April 1st,* 1957.]

[1a] Mayo, *J. Amer. Chem. Soc.*, 1943, **65**, 2324.
[16] Eley and Pepper, *Trans. Faraday Soc.*, 1947, **43**, 112.

730. *Organometallic and Organometalloidal Fluorine Compounds. Part XIII.* Trifluoromethyl Derivatives of Antimony.†*

By J. W. Dale, H. J. Emeléus, R. N. Haszeldine, and J. H. Moss.

Trifluoroiodomethane reacts with antimony at 165—170° to give the compounds $(CF_3)_3Sb$, $(CF_3)_2SbI$, and $CF_3{\cdot}SbI_2$; at higher temperatures fluorocarbons are produced. Tristrifluoromethylstibine shows markedly reduced donor properties compared with trimethylstibine, and can act as an acceptor, *e.g.*, by forming the solid $C_5H_5N,Sb(CF_3)_3$. The quinquevalent derivative, $(CF_3)_3SbCl_2$, similarly forms a 1 : 1 compound with pyridine. The preparation and certain reactions of the compounds $(CF_3)_3SbBr_2$, $(CF_3)_2SbBr$, $CF_3{\cdot}SbBr_2$, $(CF_3)_2SbCl$, $(CF_3)_2SbCl_3$, and $(CF_3)_2Sb{\cdot}Sb(CF_3)_2$ are described, and comparisons drawn with corresponding phosphorus and arsenic derivatives.

The synthesis of numerous trifluoromethyl derivatives by direct reaction of metals or metalloids with trifluoroiodomethane has been recorded in earlier Parts of this series. The preparation and properties of a series of antimony compounds are now described.

With the necessary control of temperature and pressure, reaction of trifluoroiodomethane with antimony gives mainly tristrifluoromethylstibine with smaller amounts of iodobistrifluoromethylstibine and di-iodotrifluoromethylstibine. The proportion of the iodo-compounds can be increased by use of a mixture of antimony and antimony tri-iodide at a lower reaction temperature. This suggests that a series of equilibria is involved, *e.g.*:

$$(CF_3)_3Sb + CF_3{\cdot}SbI_2 \rightleftharpoons 2(CF_3)_2SbI$$
$$(CF_3)_2SbI + SbI_3 \rightleftharpoons 2CF_3{\cdot}SbI_2$$
$$(CF_3)_3Sb + SbI_3 \rightleftharpoons (CF_3)_2SbI + CF_3{\cdot}SbI_2$$

The iodo-compounds disproportionate much more readily than the corresponding derivatives of phosphorus or arsenic,[1,2] and isolation of di-iodotrifluoromethylstibine, a viscous yellow oil, proved to be particularly difficult.

If the reaction temperature is allowed to rise above the optimum of 165—175°, fluorocarbons are produced, probably by conversion of tristrifluoromethylstibine into tetrafluoroethylene or difluoromethylene radicals, followed by combination with the CF_3 radicals arising by homolytic fission of the CF_3–Sb bond:

$$(CF_3)_3Sb \longrightarrow (CF_3)_2Sb{\cdot} + CF_3{\cdot}$$
$$(CF_3)_3Sb \longrightarrow C_2F_4 + CF_3{\cdot}SbF_2 \longrightarrow SbF_3 \text{ etc.}$$
$$(CF_3)_3Sb \longrightarrow {\cdot}CF_2{\cdot} + (CF_3)_2SbF \longrightarrow {\cdot}CF_2{\cdot} + CF_3{\cdot}SbF_2 \longrightarrow {\cdot}CF_2{\cdot} + SbF_3$$
$$CF_3{\cdot} + C_2F_4 \longrightarrow CF_3{\cdot}CF_2{\cdot}CF_2{\cdot}\ldots\ldots \longrightarrow CF_3{\cdot}[CF_2]_n{\cdot}CF_3$$
$$CF_3{\cdot} + {\cdot}CF_2{\cdot} \longrightarrow CF_3{\cdot}CF_2{\cdot} \longrightarrow CF_3{\cdot}CF_2{\cdot}CF_2{\cdot} \longrightarrow \text{etc.}$$

Carbon tetrafluoride arises by the action of antimony fluorides on trifluoroiodomethane.

Tristrifluoromethylstibine, b. p. 72° (cf. Me_3Sb, b. p. 80°), decomposes at 180°, but is stable to water at 100°; concentrated hydrochloric acid at this temperature converts it into fluoroform. As with almost all other trifluoromethyl derivatives of tervalent phosphorus, arsenic, or antimony, dilute aqueous sodium or potassium hydroxide hydrolyses tristrifluoromethylstibine to fluoroform rapidly and quantitatively at room temperature. The stibine is readily oxidised by air, but fails to react with sulphur. No reaction could be detected between tristrifluoromethylstibine (as a possible donor) and

* Part XII, *J.*, 1955, 563.

† Presented at Amer. Chem. Soc. Meeting, New York, 1954, Abs., p. 35M.

[1] Bennett, Emeléus, and Haszeldine, *J.*, 1953, 1565; 1954, 3598, 3896.

[2] Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2552; Emeléus, Haszeldine, and Walaschewski, *J.*, 1953, 1552.

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aluminium chloride, mercury chloride, or palladium chloride. The effect on antimony of the electron-attracting trifluoromethyl groups, which have at times pseudohalogen characteristics, is clearly demonstrated by the increased sensitivity to hydrolysis and by the formation of a 1 : 1 compound with pyridine, $C_5H_5N,Sb(CF_3)_3$, where antimony is clearly an acceptor; by contrast, trimethylstibine is a donor which forms complexes readily with palladium or platinous chloride.[3] Trimethylstibine does not form a complex with tristrifluoromethylstibine. Antimony trichloride also shows acceptor properties and yields complexes with ammonia, quinoline, dimethyl sulphide, and other organic donors.[4]

Tristrifluoromethylstibine shows four strong bands, at 8·43, 8·75, 8·91, and 9·17 μ, in the C–F stretching vibration region and a strong band at 13·85 μ attributed to CF_3 deformation [cf. $(CF_3)_3P$ 13·3; $(CF_3)_3As$ 13·6 μ].

Tristrifluoromethylstibine reacts smoothly and exothermally with chlorine at −45° to give tristrifluoromethylantimony dichloride, $(CF_3)_3SbCl_2$; reaction at higher temperatures causes loss of chlorotrifluoromethane. There is a marked contrast between the labile, liquid tristrifluoromethylantimony dichloride and trimethylantimony dichloride, a white solid decomposing only at 150—200°. Tristrifluoromethylantimony dichloride is hydrolysed immediately with aqueous alkali according to the equation:

$$(CF_3)_3SbCl_2 + 3NaOH \longrightarrow Na[(CF_3)_3Sb(OH)_3] + 2NaCl$$

The properties of tristrifluoromethylantimonic acid and its salts have been described earlier.[5] Tristrifluoromethylantimony dichloride forms a 1 : 1 complex with pyridine. Antimony pentachloride, but not phosphorus pentachloride, is known to form many stable 1 : 1 complexes, including those with water, ether, and pyridine.[6] Antimony pentabromide [7] can exist as the six-co-ordinated etherate $Et_2O,SbBr_5$, whereas phosphorus pentabromide [8] is in the four-co-ordinate form $PBr_4^+Br^-$. Attempts to form complexes of tristrifluoromethylantimony dichloride with phosphorus pentachloride, aluminium chloride, or auric chloride were unsuccessful, although the compound $SbCl_5,AuCl_3$, formulated as $SbCl_4^+AuCl_4^-$, has been described.[9]

Mercury reconverts tristrifluoromethylantimony dichloride into tristrifluoromethylstibine quantitatively.

The reaction of bromine with tristrifluoromethylstibine is more difficult to control. At −30° tristrifluoromethylantimony dibromide is formed, whereas reaction at 20° gives bromobistrifluoromethylstibine, dibromotrifluoromethylstibine, and bromotrifluoromethane. Tristrifluoromethylantimony dibromide decomposes when kept at room temperature:

$$(CF_3)_3SbBr_2 \longrightarrow CF_3Br + (CF_3)_2SbBr$$

Bromobistrifluoromethylstibine disproportionates only slowly when kept:

$$2(CF_3)_2SbBr \rightleftharpoons (CF_3)_3Sb + CF_3{\cdot}SbBr_2$$
$$2CF_3{\cdot}SbBr_2 \rightleftharpoons (CF_3)_2SbBr + SbBr_3$$

Iodobistrifluoromethylstibine is best prepared from tristrifluoromethylstibine by reaction with iodine or antimony tri-iodide; it readily disproportionates on exposure to heat or light to give products analogous to those from the bromo-compound.

The iodine atom is reactive, as in the corresponding phosphorus or arsenic compounds,

[3] Morgan and Yardley, *J.*, 1925, **127**, 184.
[4] Rose, *Pogg. Ann.*, 1830, **20**, 160; Schiff, *Annalen*, 1864, **131**, 116; Adhikari, Ray, and Roy, *J. Indian Chem. Soc.*, 1931, **8**, 715.
[5] Emeléus and Moss, *Z. anorg. Chem.*, 1955, **282**, 24.
[6] Anschutz and Evans, *Annalen*, 1887, **239**, 291; Williams, *Trans. Faraday Soc.*, 1876, **30**, 463.
[7] Raynaud, *Bull. Soc. chim. France*, 1920, **27**, 411.
[8] Van Driel and Macgillavry, *Rec. Trav. chim.*, 1943, **62**, 167.
[9] Sidgwick, "The Chemical Elements and Their Compounds," Clarendon Press, Oxford, 1950, p. 191.

but disproportionation often occurs faster than a simple replacement reaction. Silver chloride gives chlorobistrifluoromethylstibine, a compound that disproportionates readily to tristrifluoromethylstibine and antimony trichloride.

Further reaction of iodobistrifluoromethylstibine with iodine at room temperature gives di-iodotrifluoromethylstibine:

$$(CF_3)_2Sb \xrightarrow{I_2} (CF_3)_2SbI \xrightarrow{I_2} CF_3{\cdot}SbI_2 + SbI_3(+ CF_3I)$$

Mercury or, better, zinc reacts with iodobistrifluoromethylstibine to give tetrakistrifluoromethyldistibine. The boiling points of this and other stibines are compared with the corresponding nitrogen, phosphorus, and arsenic compounds in the annexed Table.

Boiling points of some trifluoromethyl compounds.

Element (M):	N	P	As	Sb
$(CF_3)_3M$	−11°	17°	33°	72°
$(CF_3)_2MI$	—	73	92	*ca.* 129
$CF_3{\cdot}MI_2$	—	153	183	>200
$(CF_3)_2MCl$	—	21	46	*ca.* 88
$(CF_3)_2MBr$	—	—	60	113
$CF_3{\cdot}MBr_2$	—	—	118	155
$[(CF_3)_2M\cdot]_2$	20°/95 mm.	84	107	*ca.* 136
$(CF_3)_3MCl_2$	—	94	98	*ca.* 101
$(CF_3)_2MCl_3$	—	107	95	13°/5 mm.*

* Vapour pressure of the solid.
Cf. Me_2SbCl, b. p. 155—160°; Me_2SbBr, b. p. 175—180°; $(Me_2Sb)_2$, b. p. 190°.

Trifluoromethyl derivatives of tervalent antimony boil 30—50° higher than the corresponding arsines and 50—60° higher than the phosphines. The analogous methylstibines are often solids at room temperature and have much higher boiling points. The relatively slight increase in boiling point in the series $(CF_3)_3MCl_2$ as the element (M) increases in atomic weight is noteworthy.

Tetrakistrifluoromethyldistibine is a pale yellow liquid unlike its methyl analogue, which is a bright red solid melting to a yellow oil.

Tetrakistrifluoromethyldistibine liberates almost the whole of its fluorine as fluoroform on hydrolysis with aqueous alkali, and only 1—2% [cf. 9% for $(CF_3)_2P{\cdot}P(CF_3)_2$ and 16% for $(CF_3)_2As{\cdot}As(CF_3)_2$][1,2] as fluoride. Reaction of tetrakistrifluoromethyldistibine with an excess of bromine or iodine at higher temperatures yields bromotrifluoromethane or trifluoroiodomethane; chlorine cleaves the Sb–Sb bond at −78° to form the trichloride $(CF_3)_2SbCl_3$. In many ways, tetrakistrifluoromethyldistibine is a more convenient source of bistrifluoromethylantimony derivatives than is iodobistrifluoromethylstibine.

The trifluoromethyl derivatives of tervalent antimony are thus prepared from trifluoroiodomethane with distinctly greater difficulty than the corresponding phosphorus or arsenic compounds, and are appreciably less stable thermally; the metal–carbon bond becomes weaker as the atomic weight of the metal or metalloid increases within the group. The reactions of tristrifluoromethylstibine with the halogens, by addition and/or substitution, resemble those of tristrifluoromethyl-phosphine or -arsine. Antimony reaches the quinquevalent state more easily than arsenic, however, and this is shown in its trifluoromethyl derivatives. Tristrifluoromethylarsenic dichloride is known, but attempts to make the bromide $(CF_3)_3AsBr_2$ failed.[2] The existence of tristrifluoromethylantimony dibromide but not of antimony pentabromide suggests that quinquevalent antimony is more stable in its trifluoromethyl derivatives than in its fully inorganic halides. Quinquevalent antimony appears to be most stable in its alkyl compounds, however, since trimethylantimony di-iodide has been reported.[10] All attempts to make tristrifluoromethylantimony di-iodide failed; there was no reaction between tristrifluoromethylstibine and

[10] Landolt, *Annalen*, 1852, **84**, 44.

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iodine at low temperatures, and cleavage to give trifluoroiodomethane occurred at higher temperatures (*ca.* 20°). The ease of such cleavage increases with the atomic weight of the group VB elements: tristrifluoromethylphosphine reacts with iodine at 180° and tristrifluoromethylarsine at 100°.

EXPERIMENTAL

Reactions were carried out in sealed tubes unless otherwise stated, and conventional vacuum-techniques were used for the manipulation of volatile products. Where possible, the antimony compounds were analysed by treatment with 10% aqueous potassium hydroxide at 70° for 24 hr. to give fluoroform quantitatively; this was distilled *in vacuo* and weighed. Ionic fluorine was determined by titration with thorium nitrate, and covalent fluorine by fusion with sodium followed by steam-distillation of the acidified solution and titration with thorium nitrate. Antimony was determined by the iodine or bromate method. Molecular weights were determined by Regnault's method.

Reaction of Antimony with Trifluoroiodomethane.—Preliminary experiments showed that Pyrex tubes were unsuitable as reaction vessels since extensive attack on the glass occurred. The most suitable apparatus was found to be a 300 ml. steel cylinder to which were added coarsely ground antimony (50—100 g.) and trifluoroiodomethane (75—120 g.). The cylinder was sealed and rotated in a horizontal position for 3—10 hr. whilst immersed in an oil-bath. Little reaction occurred at <160°, and 165—175° was the optimum temperature with this size of apparatus. This is distinctly lower than the temperature required for the preparation of the corresponding phosphorus or arsenic compounds. Rotation of the cylinder prevents sintering of the antimony tri-iodide which cuts down the surface area of the antimony considerably and so prevents further reaction. Use of a high pressure (>50 atm. calc.) was found necessary for good yields.

In a typical experiment, antimony (100 g.) and trifluoroiodomethane (75 g.) heated at 165—170° for 7 hr. gave a mixture (30 g.) of trifluoromethylantimony compounds containing approx. 90% of tristrifluoromethylstibine and 10% of iodobistrifluoromethylstibine; with a different ratio, antimony (50 g.) and trifluoroiodomethane (110 g.) gave 18 g. of crude product (90% yield based on trifluoroiodomethane consumed). Distillation of the crude product obtained from several experiments of the above type gave *tristrifluoromethylstibine* (Found: CF_3, 63·2; Sb, 37·1%; *M*, 328. C_3F_9Sb requires CF_3, 63·0; Sb, 37·0%; *M*, 329), b. p. 72°, *iodobistrifluoromethylstibine* (Found: CF_3, 35·7; I, 32·8; Sb, 31·7. C_2F_6ISb requires CF_3, 35·7; I, 32·8; Sb, 31·5%), b. p. 16°/8 mm., m. p. −42°, and impure di-iodotrifluoromethylstibine (Found: CF_3, 14·0; I, 56·2; Sb, 26·8. Calc. for CF_3I_2Sb: CF_3, 15·5; I, 57·1; Sb, 27·4%), m. p. 4—8°, b. p. >200° (with disproportionation).

The solid residue in the cylinder contained antimony tri-iodide, isolated by sublimation *in vacuo* (Found: I, 75·4; Sb, 24·0. Calc. for SbI_3: I, 75·7; Sb, 24·3%), m. p. 168°. Qualitative tests for fluoride were positive, but there were no quinquevalent antimony compounds present, and treatment of the solid with aqueous alkali failed to liberate fluoroform.

Reaction at temperatures above the optimum caused extensive side-reactions; at 200°, for example, about 75% of the liquid product was fluorocarbon [Found: F, 76·1. Calc. for $(CF_2)_n$: F, 76·0%], b. p. range −40° to 150°, showing the typical infrared spectrum and chemical and thermal stability of this type of compound.

Reaction of fresh antimony with trifluoroiodomethane at the optimum temperature gave *ca.* 10% of the liquid product as iodobistrifluoromethylstibine; if the antimony, now containing antimony tri-iodide, was used in subsequent reactions with trifluoroiodomethane, the iodobistrifluoromethylstibine content of the liquid product increased to 25%. The yield of the iodostibine was higher at 165° than at 175°.

The first experiment with fresh antimony in a clean reaction vessel always gave low yields, but the second experiment with fresh antimony gave good yields; this is attributed to the decomposition of trifluoroiodomethane on the walls and to the deposition of antimony tri-iodide on the walls of the vessel, thus providing a protective coating for the second experiment.

Tristrifluoromethylstibine.—The vapour pressure p of this colourless mobile liquid is given by the expression $\log_{10} p$ (mm.) = 7·031 − 1811/T, where T is the temperature in °K, whence the b. p. is 71·7° and Trouton's constant is 24·0. The m. p. is −58°. The liquid is oxidised in air with formation of white fumes of carbonyl fluoride and carbon dioxide, and the exothermic

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reaction will ignite a 0·2 ml. sample of the liquid, or produce a mild explosion in the vapour. Tristrifluoromethylstibine is stable at 160° *in vacuo* and is not decomposed on exposure to daylight.

Tristrifluoromethylstibine (2·19 g.) is insoluble in water (5 ml.) and is recovered unchanged after being heated with it at 100° for 8 hr. The stibine (1·70 g.) was unaffected by concentrated hydrochloric acid (5 ml.) at 20°, but completely destroyed by it after 6 hr. at 100° to give fluoroform (0·99 g., 90%) and fluoride. The stibine was hydrolysed quantitatively to fluoroform and antimonite by 2N-aqueous potassium hydroxide at 20° during 24 hr.

Trifluoromethylstibine failed to react with sulphur between −40° and 100°, though sulphur is appreciably soluble in the stibine at 100°. There was no reaction with aluminium chloride or palladous chloride at 20° (24 hr.).

Pyridine (0·027 g.) and tristrifluoromethylstibine (0·192 g.) reacted as the mixture warmed from −80°, to give white crystals soluble in the excess of the stibine as the temperature increased. The unchanged tristrifluoromethylstibine was removed at 0° by pumping, to leave *tristrifluoromethylstibine–pyridine* (Found: CF_3, 50·5. $C_8H_5NF_9Sb$ required CF_3, 50·8%) as a white solid, m. p. 39°. The vapour pressure of the liquid is given by the equation $\log_{10} p$ (mm.) = 8·713 − 2740/T whence the b. p. is approx. 127°. The high value of 31 obtained for Trouton's constant from this equation suggests that the compound dissociates in the vapour phase, as often found with weak complexes.

Reaction of Tristrifluoromethylstibine with Halogens.—(a) *With chlorine.* Tristrifluoromethylstibine (0·874 g.) was treated with nine successive portions of chlorine (0·189 g., total) at −40° to −50°. Each addition caused an exothermic reaction, and the mixture was cooled before addition of the next portion of chlorine to prevent explosive decomposition. Distillation *in vacuo* gave *tristrifluoromethylantimony dichloride* (1·053 g.) (Found: CF_3, 51·8; Cl, 17·7; Sb, 29·9%; M, 401. $C_3Cl_2F_9Sb$ requires CF_3, 51·8; Cl, 17·7; Sb, 30·4%; M, 400) as a colourless liquid, m. p. −34°, whose vapour pressure is given by the equation $\log_{10} p$ (mm.) = 7·290 − 2024/T between −30° and 50°, whence the extrapolated b. p. is 101°. The chloro-compound decomposes slowly at 20°, more rapidly at 50° and above to give chlorotrifluoromethane. It is stable in dry air.

Tristrifluoromethylantimony dichloride (0·122 g.) and mercury (10·4 g.), shaken for 15 min., gave tristrifluoromethylstibine (0·099 g.) (Found: M, 326. Calc. for C_3F_9Sb: M, 329), and mercury chlorides.

Reaction of the chloro-compound (0·660 g.) with pyridine (0·054 g.) followed by pumping for 30 min. gave the white infusible solid *tristrifluoromethylantimony dichloride–pyridine* (0·301 g.) (Found: CF_3, 42·9. $C_8H_6NCl_2F_9Sb$ requires CF_3, 43·2%).

(b) *With bromine.* Tristrifluoromethylstibine (0·798 g.) dissolved bromine (0·362 g.) slowly at −30°, to give the unstable yellow *tristrifluoromethylantimony dibromide* (Found: CF_3, 42·8; Br, 32·9; Sb, 24·9. $C_3Br_2F_9Sb$ requires CF_3, 42·4; Br, 32·7; Sb, 24·9%), m. p. −16°, purified by trap-to-trap distillation *in vacuo*. Bromotrifluoromethane is not liberated during this reaction.

Reaction of the stibine (13·8 g.) with bromine (7·2 g.) by mixing at −30° then warming to 20° gave, after 17 hr., tristrifluoromethylstibine (5·40 g.), *bromobistrifluoromethylstibine* (4·9 g.) (Found: CF_3, 40·7; Br, 23·7. C_3BrF_6Sb requires CF_3, 40·7; Br, 23·6%), b. p. 113°, *dibromotrifluoromethylstibine* (1·9 g.) (Found: CF_3, 19·9; Br, 45·0. CBr_2F_3Sb requires CF_3, 19·7; Br, 45·6%), b. p. 34°/2·5 mm., *ca.* 155°/760 mm., bromotrifluoromethane, and antimony tribromide.

(c) *With iodine.* Powdered iodine (0·383 g.) gave a pale violet solution in tristrifluoromethylstibine (1·171 g.), deepening to brown, when shaken with it in a sealed 50 ml. tube. The colour soon faded and after 30 min. all the iodine had dissolved, to give an orange-yellow solution with deposition of a red solid and evolution of a gas. Fractionation, carried out immediately to minimise disproportionation of the products, gave trifluoroiodomethane (Found: M, 195. Calc. for CF_3I: M, 196), tristrifluoromethylstibine, iodobistrifluoromethylstibine (0·314 g., 54%) with an infrared spectrum identical with that of the material described earlier, crude di-iodotrifluoromethylstibine (14%) (Found: CF_3, 16·3; I, 55·5; Sb, 26·0. Calc. for CF_3I_2Sb: CF_3, 15·5; I, 57·1; Sb, 27·4%) as a yellow oil, and antimony tri-iodide. This is the best method for preparation of iodobistrifluoromethylstibine.

Tristrifluoromethylstibine (0·20 g.) and antimony tri-iodide (3·0 g.), heated at 120° for 7 days in a 15 ml. sealed tube, gave iodobistrifluoromethylstibine, identified spectroscopically, along with unchanged tristrifluoromethylstibine and antimony tri-iodide.

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Iodobistrifluoromethylstibine decomposes rapidly when heated, particularly in light. A sample (0·206 g.) kept for 6 months in the dark at 20° gave tristrifluoromethylstibine (0·055 g.), unchanged iodobistrifluoromethylstibine (0·101 g.), di-iodotrifluoromethylstibine (0·004 g.), and antimony tri-iodide (0·039 g.). Traces of air or alkali catalyse the disproportionation.

Di-iodotrifluoromethylstibine is a viscous bright yellow liquid which freezes to a pale yellow solid. It is stable to water but decomposed readily by aqueous potassium hydroxide with evolution of fluoroform. Disproportionation occurs slightly less readily at room temperature than for iodobistrifluoromethylstibine, but is rapid on attempted distillation at atmospheric pressure.

Chlorobistrifluoromethylstibine.—Iodobistrifluoromethylstibine (0·534 g.) and silver chloride (2·02 g.), kept in a sealed tube at room temperature for 24 hr., gave crude chlorobistrifluoromethylstibine (0·411 g.) (Found: CF_3, 46·8%; *M*, 292. Calc. for C_2ClF_6Sb: CF_3, 46·8%; *M*, 295). A satisfactory chlorine analysis could not be obtained for this compound, and attempts to purify it further were unsuccessful since it disproportionates rapidly to tristrifluoromethylstibine and antimony trichloride. Chlorobistrifluoromethylstibine is a colourless liquid of vapour pressure 20 mm. at 17° and b. p. approx. 88°; it is hydrolysed only slowly by hot water to give antimony trioxide, and rapidly by aqueous sodium hydroxide to give fluoroform, chloride, and antimonite.

Tetrakistrifluoromethyldistibine.—Reaction of iodobistrifluoromethylstibine, or of the crude liquid products from the reaction of trifluoroiodomethane with antimony, with an excess of zinc powder or mercury gave *tetrakistrifluoromethyldistibine* almost quantitatively [Found: F, 43·6% (42·9% as CHF_3, 0·7% as F^-); Sb, 46·7%; *M*, 514. $C_4F_{12}Sb_2$ requires F, 43·9; Sb, 47·0%; *M*, 518], b. p. 16·8°/4·1 mm., 28·3°/10·3 mm., 34°/14·1 mm., approx. 136°/760 mm. The reaction with mercury is relatively slow and is incomplete after 3 days' shaking. Tetrakistrifluoromethyldistibine is a pale yellow liquid which deepens in colour when heated, and freezes to a colourless solid. It slowly decomposes at room temperature, particularly in light. It is readily oxidised by air and is insoluble in, and denser than, water. Hydrolysis with aqueous potassium hydroxide liberated the fluorine as fluoroform and fluoride ion, and yielded antimony and antimonite. For determination of antimony the compound was first decomposed by treatment with an excess of bromine at 20° (24 hr.) to give bromotrifluoromethane and antimony tribromide; the antimony content of the solid was determined in the usual way.

Tetrakistrifluoromethyldistibine (3·23 g.) dissolved in trichlorofluoromethane (9 g.) at −78° to a colourless solution to which chlorine was added portionwise until a pale yellow colour in the liquid revealed the presence of a slight excess. The exothermic reaction produced a white solid, isolated by removal of the more volatile products *in vacuo* at −46°, then purified by fractionation *in vacuo* and shown to be *bistrifluoromethylantimony trichloride* (Found: CF_3, 37·8; Cl, 28·6; Sb, 33·1. $C_2Cl_3F_6Sb$ requires CF_3, 37·7; Cl, 29·1; Sb, 33·2%), b. p. 13°/5 mm., m. p. 27°. The solid slowly decomposes to give chlorotrifluoromethane at 25°, but can be stored indefinitely at −78°.

Reaction of tetrakistrifluoromethyldistibine with an excess of iodine in a sealed tube at 90° for 24 hr. gave antimony tri-iodide and trifluoroiodomethane essentially quantitatively. Bromine attacks the distibine at room temperature to liberate bromotrifluoromethane and antimony tribromide quantitatively.

One of us (J. H. M.) is indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance. Grateful acknowledgment is made to the Canadian Defence Research Board for leave of absence and a scholarship (to J. W. D.).

CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 16th*, 1957.]

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731. *The Formation of Ketones. Part III.* The Pyrolysis of Sodium Acetate and Some Sodium Dicarboxylates.*

By R. I. Reed and (Miss) M. B. Thornley.

Decomposition of the molten sodium salts of acetic and α- and β-methyladipic acid is shown to be of simple, integral kinetic order, suggesting that the reactions proceed by an ionic mechanism. There is evidence for mild catalysis by carbon in all cases. Decomposition of sodium adipate, however, has the kinetic characteristics of an autocatalytic reaction; the presence of carbon, normally a by-product, has a marked effect on the course of the reaction. The distinctive behaviour of this compound is considered to be a consequence of the physical state of the salt which only softens at reaction temperatures. Variations in the velocity constants of the decomposition of the sodium salts of acetic and α- and β-methyladipic acids support a one-stage mechanism.

The mechanism of the pyrogenic formation of cyclic ketones, as a particular type of Claisen condensation, was proposed by Neunhoeffer and Paschle [1] from a study of the decomposition of barium and calcium adipate, and was supported by Wiberg's investigations.[2] Other theories have been discussed by the above authors, and by Kenner and Morton,[3] and Lee and Spinks.[4] Some evidence in favour of an ionic mechanism of reaction has been adduced from isotopic studies [5] on the formation of ketones by passing the appropriate acids over a suitable catalyst. Recent kinetic studies on systems of this type have led to the conclusion that a salt is first formed,[6] at least in the case of acetic acid passed over heated thoria.

The present studies, which support the view that the reaction proceeds substantially by an ionic mechanism, have been undertaken on sodium acetate and some sodium dicarboxylates. In most cases mild catalysis by carbon was found. Rate constants for sodium acetate were obtained by two methods: first, by measuring the loss in weight of a sample caused by the escape of the reaction product, acetone, and, secondly, by estimating the quantity of sodium acetate remaining at suitable intervals during the reaction (Experiments 6 and 7. Table 1). Substantial agreement was obtained between the two methods.

Table 1. *Pyrolysis of sodium acetate.**

No.	Temp.	$10^3k_2'$ (mole min.$^{-1}$) †	No.	Temp.	$10^3k_2'$ (mole min.$^{-1}$) †
1 [a]	428°	6·50 ± 0·18	5 [b]	452°	24·39 ± 0·28
2	430	6·32 ± 0·16	6 [c]	429	6·59 ± 1·3
3	440	9·97 ± 0·21	7 [d]	429	9·52 ± 2·1
4	452	15·68 ± 0·24			

* In a platinum vessel, unless otherwise stated.
† The ± figures are standard deviations.
[a] Silica reaction vessel. [b] Platinum vessel, 9·53% by wt. of added carbon. [c] Glass reaction vessel. [d] Glass reaction vessel, 10% by wt. of added carbon.

As these experiments were conducted on melts, in which condition it is not possible to vary the initial concentration of the salt, a full formal examination of the reaction order with respect to the salt was not undertaken. Within any given experiment,

* Part II, *J.*, 1954, 2148.

[1] Neunhoffer and Paschke, *Ber.*, 1939, **72**, 919.
[2] Wiberg, *J. Amer. Chem. Soc.*, 1952, **74**, 4381.
[3] Kenner and Morton, *Ber.*, 1939, **72**, 452.
[4] Lee and Spinks, *J. Org. Chem.*, 1953, **18**, 1079; *Canad. J. Chem.*, 1953, **31**, 103.
[5] Reed, *J.*, 1955, 4423.
[6] Kuriacose and Jungers, *Bull. Soc. chim. belges*, 1955, **64**, 502.

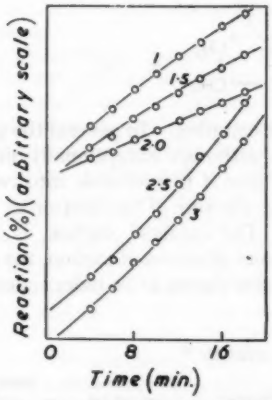
however, the calculated second-order velocity constants showed good agreement with no evidence of a progressive drift in values, as is shown in Fig. 1, where the data are fitted to reaction orders of 1, 1·5, 2, 2·5, and 3 severally.

If the reaction is assumed to be between two molecules or acetate ions, its rate will be proportional to the square of the amount of reactant present. This leads to a second-order rate constant. The intramolecular decomposition of a dicarboxylate would give a first-order rate constant.

Sodium carbonate formed in the reaction does not separate, being somewhat soluble in the melt, until after ~10% reaction. When deposition does begin, however, there is no discontinuity in the reaction–time graph until the reaction is at least 75% completed.

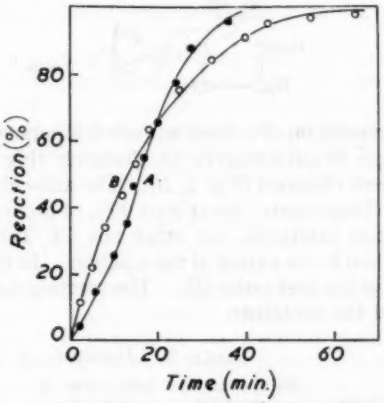
The results show mild catalysis by added carbon, the rate being increased 1·45 and 1·56 times respectively. Further large additions of carbon did not affect this value.

FIG. 1.



○ *Experimental values plotted for the various reaction orders marked on the curves.*

FIG. 2.



A, Autocatalytic reaction. B, First-order reaction. ○ *Experimental values.* ● *Calculated values.*

Similar studies on sodium α- and β-methyladipate which, like sodium acetate, melt before decomposition, are reported in Table 2. Arguments analogous to those used above for sodium acetate show these results to represent first-order reactions, and to support an ionic mechanism of reaction. Further it may be expected that molecules of this type would cyclise with great facility. Again mild catalysis by carbon was observed, the maximum rate increases for sodium β-methyladipate being 1·48—1·54 times.

TABLE 2. *Pyrolysis of disodium α- and β-methyladipates.**

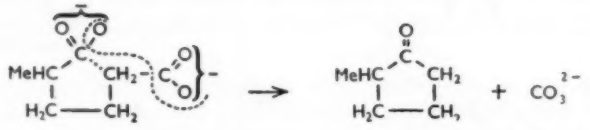
No.	Temp.	10^3k_1 (min.$^{-1}$)	No.	Temp.	10^3k_1 (min.$^{-1}$)	No.	Temp.	10^3k_1 (min.$^{-1}$)
α-Methyl derivative			β-Methyl derivative			β-Methyl derivative		
8	405°	1·12 †	12	395°	1·06 †	16	427°	8·40 †
9	410	1·67	13	410	2·89	17 ‖	427	12·44
10	415	2·36	14 ‡	427	8·24	18 ‖	427	13·01
11	419	3·15	15 ƒ	427	8·35			

* Unless otherwise stated, a platinum bucket was used.
† The standard deviation in all cases is less than ±0·02.
‡ Silica vessel. ƒ Salt mixed with 10% of sodium carbonate. ‖ Salt mixed with 11% of carbon.

It is difficult to compare directly the rate constants for the decomposition of these salts and sodium acetate because the reaction orders differ. Some comparison can however be made by deriving an initial rate for sodium acetate as the product of the velocity

constant and the initial concentration of the salt. By comparing the extrapolated value at 410° with velocity constants for the other salts at this temperature the series of relative reactivities β 2·89, α 1·67, Ac 0·42 is obtained, in accord with general theory. The dicarboxylates which yield *cyclo*pentanones are considered to cyclise very easily,[7] and a β-methyl substituent favours the process.[8]

The mechanism most recently proposed, that of Lee and Spinks,[4] seems inadequate to explain these results, depending as it does upon so many particular steric considerations, although its one-stage process seems more probable than a two-stage ionisation process. Accordingly it is suggested that a one-stage reaction of the annexed form is an adequate representation, at least on present evidence. The electron-releasing methyl group will facilitate separation of the O^- to complete the reaction. This would lead to a stronger effect by the α- than by the β-Me methyl group, but the influence of the latter on the molecular geometry, favouring closure, outweighs the electronic effects.



Decomposition of sodium adipate is kinetically more complex. In general the product–time graph is autocatalytic in character (Fig. 2, *A*), although exceptionally first-order graphs were obtained (Fig. 2, *B*). The autocatalytic curve *A* is resolvable into two parts, and is well represented for at least 90% of the reaction as the sum of two first-order velocity graphs, one catalysed, the other not (cf. Table 3). The catalyst, carbon, is assumed proportional to the extent of the reaction. In the presence of excess of carbon, the reaction becomes of the first order (*B*). The reaction rate was also shown to be independent of the surface of the container.

TABLE 3. *Pyrolysis of sodium adipate.**

No.	Temp.	10^3k_1 (min.$^{-1}$) (uncat.) †	10^3k_1 (min.$^{-1}$) (cat.) †	No.	Temp.	10^3k_1 (min.$^{-1}$) (uncat.) †	10^3k_1 (min.$^{-1}$) (cat.) †
19	430°	0·16	—	23	440°	1·34	4·38
20	440	1·34	3·88	24 [h]	440	1·50	3·84
21	449	3·90	7·08	25 [i]	440	1·39	3·43
22	464	6·96	14·76	26 [j]	440	—	3·08

* Unless otherwise stated, the reactions were carried out in a platinum vessel.
† Standard deviations in all cases, except No. 19 (±0·04), were less than ±0·02.
[h] Silica vessel. [i] Pyrex vessel. [j] Pyrex vessel coated with carbon.

Catalysis is rather greater than that in the previous examples and is considered a consequence of the physical state of the reacting material. Sodium adipate does not melt below the temperature of decomposition and examination of the crystals supports the conclusion that during reaction there is at most some softening, the crystals nevertheless retaining their shape. Consequently, it is considered that at least one function of the carbon present is to lower the energy necessary for the escape of the ketone from the crystal. It has not, as yet, been possible to demonstrate any other function of the carbon. Some mobility of reacting entities within crystals and across their boundaries seems necessary, however, to account for the observation that a layer of carbon on the walls of the vessel is as efficient a catalyst as a sample intimately mixed with the solid adipate.

EXPERIMENTAL

These experiments were conducted in a sodium nitrate–potassium nitrate melt, the temperature of which was thermostatically controlled. The appropriate salt was put in the bucket

[7] Bennett, *Trans. Faraday Soc.*, 1941, **37**, 794.
[8] Reed and Thornley, *J.*, 1954, 2150.

of a modified sorption balance [9] and there pyrolysed. The temperature control was based upon a mechanical lever operated by the expansion of a metal rod, and preliminary experiments showed that the temperature at the centre of the bath was constant within 0·5° provided the bath-liquid was rapidly stirred and the rate of heating about balanced the heat loss. The salt was contained in a shallow boat of platinum, Pyrex, or silica, and heated by a stream of nitrogen, preheated by passage through a spiral immersed in the thermostat. The progress of the reaction was followed by measuring the loss in weight of the bucket determined by the extension of a spring, which had previously been calibrated at the temperature of the experiment and was further checked by weighing the boat and contents before and after reaction. The extent of reaction was determined by titrating the residual carbonate and weighing the carbon formed.

Preliminary examination of the apparatus for heat-transport effects suggested that, provided less than 0·3 g. of material was taken, these were without effect upon the reaction velocity. Usually less than half this quantity of salt was used.

Mixtures of sodium adipate and carbonate were obtained by evaporating a solution of the mixture, drying the residue, and grinding it to a fine powder. In the case of the carbon catalyst, the required quantity of this and the salt were ground together to a fine powder.

In addition to experiments with the sorption balance, some on sodium acetate were carried out as follows.

Equal quantities of about 0·1 g. of sodium acetate were weighed out, and some samples were mixed with 10% of their weight of carbon. The samples were placed in Pyrex tubes, dried at 110°, and sealed under a oil-pump vacuum. The pyrolyses were carried out at 428°, tubes being withdrawn at suitable time intervals and quenched in water. This solution was made up to 100 ml. and analysed by the method of Hutchen and Kass,[10] using a Hilger " Spekker " absorptiometer: comparison of the unknown with known standards of about the same concentration was necessary for reliable results.

The results were in good agreement. Product analyses were also carried out by trapping the ketone evolved in certain experiments and preparing the 2 : 4-dinitrophenylhydrazone [11] which was then weighed. Yields of over 98% were obtained in all cases.

Materials.—Sodium adipate. Adipic acid (British Drug Houses Ltd.) recrystallised twice from water had m. p. 150°. An aqueous solution was neutralised with a calculated amount of " AnalaR " sodium hydroxide and evaporated to dryness, the residue being powdered.

Sodium α-methyladipate. α-Methyladipic acid, the minor product from the oxidation of 3-methyl*cyclo*hexanone,[12] was repeatedly recrystallised from water (m. p. 59°), and made into the salt as above.

Sodium β-methyladipate. β-Methyladipic acid, the major product from the above oxidation, was salted out by ammonium nitrate, repeatedly recrystallised from water (m. p. 94·5°), and treated as above.

Carbon. Sugar charcoal was finely ground, boiled with water, filtered off, and dried.

Other materials used were of the highest possible purity, " AnalaR " where possible.

The authors express their gratitude to Mr. R. S. McCulloch for the construction and maintenance of the high-temperature thermostat.

UNIVERSITY OF GLASGOW. [*Received, November 14th,* 1956.]

[9] Reilly and Rae, " Physico-Chemical Methods," Methuen and Co., 1948, Vol. III (Supplementary), p. 267.
[10] Hutchen and Kass, *J. Biol. Chem.*, 1949, **177**, 571.
[11] Iddles and Jackson, *Ind. Eng. Chem. Anal.*, 1934, **6**, 456; Iddles, Low, Rosen, and Hart, *ibid.*, 1939, **11**, 102.
[12] Markovnikoff, *Chem. Zentr.*, 1903, **2**, 289.

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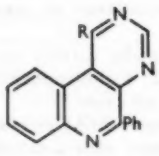
732. *Triazaphenanthrenes. Part I. Derivatives of* 10-*Phenyl*-1 : 3 : 9-*triazaphenanthrene.*

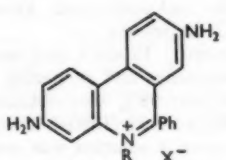
By C. M. Atkinson and A. R. Mattocks.

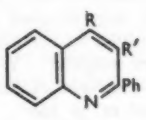
Various 4-substituted derivatives (I) of 10-phenyl-1 : 3 : 9-triazaphenanthrene have been prepared. Monomethiodides of the compounds (I; R = H or NH_2) were found to be biologically inactive; attempts to prepare an *N*-oxide yielded only hydroxy-compounds.

The preparation of salts derived from compounds of type (I) was undertaken in order to compare the biological activity with that of the related phenanthridinium compounds (II). These have been used extensively in the treatment of trypanosomiasis (II, R = Me as dimidium; R = Et as ethidium), and their effectiveness as prophylactic agents when administered as sparingly soluble complexes with suramin [1] has given added interest to this investigation.

The key intermediate for the present work, 3-amino-2-phenylquinoline-4-carboxylic acid (III; R = CO_2H, R′ = NH_2) was best prepared *via* the 3-phthalimido-derivative [incorrectly formulated as the 3-phthalamic acid (III; R = CO_2H, R′ = $NH{\cdot}CO{\cdot}C_6H_4{\cdot}CO_2H$)


(I)


(II)


(III)

by Berlingozzi and Marzella [2] rather than *via* the 3-benzamido-compound [3] since the yields from phenacyl bromide of the precursors (phenacylphthalimide and benzoylphenacylamine) were found to be 80% and 26%, respectively. The subsequent Pfitzinger reaction with isatin gave an 80% yield of the substituted quinoline. Experiments on the dephthaloylation of [III; R = CO_2H, R′ = $N(CO)_2C_6H_4$] did not support the claims made in the literature: Berlingozzi and Marzella's method gave a mixture of 3-amino-2-phenylquinoline-4-carboxylic acid and the product of subsequent decarboxylation in poor yield. Boiling sulphuric acid had little effect unless more concentrated than 50% (v/v) in which simultaneous hydrolysis and decarboxylation occurred; and hot phosphoric acid caused only decarboxylation. However, the amino-acid (III; R = CO_2H, R′ = NH_2) was readily obtained by treatment of the phthaloyl derivative with hydrazine in acetic acid.

4-Hydroxy-10-phenyl-1 : 3 : 9-triazaphenanthrene (I; R = OH), prepared from the amino-acid (III; R = CO_2H, R′ = NH_2) and formamide, was converted into the chloro-compound by prolonged heating in a sealed tube with phosphorus pentachloride; less drastic conditions gave undesired products. The amine (I; R = NH_2) could be prepared directly from the chloro-compound or *via* the phenoxy-derivative (I; R = OPh); it could also be made from 3-amino-4-cyano-2-phenylquinoline and formamide (cf. the synthesis of 4-aminopyrazolo[3,4-*d*]pyrimidine from 3-amino-4-cyanopyrazole and boiling formamide [4]): a derived monomethiodide was inactive against hæmolytic *Streptococcus, Staph. aureus,*

[1] Williamson and Desowitz, *Nature*, 1956, **177**, 1074.
[2] Berlingozzi and Marzella, *Atti Acad. naz. Lincei, Rend. Classe Sci. fys. mat. nat.*, 1923, **32**, ii, 403.
[3] Petrow, Stack, and Wragg, *J.*, 1943, 316.
[4] Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784.

B. coli, *Candida albicans*, *P. berghei*, *B. rodhaini*, *T. equiperdum*, *T. congolense*, and *T. cruzi*, when tested by Dr. F. Hawking and his colleagues.

The hydroxy-compound (I; R = OH), on treatment with dimethyl sulphate, gave an *N*-methyl derivative, distinct from the *O*-methyl compound obtained from the chloro-derivative (I; R = Cl) and sodium methoxide.

10-Phenyl-1 : 3 : 9-triazaphenanthrene (I; R = H) was prepared *via* the toluene-*p*-sulphonhydrazide (cf. Albert and Royer [5]) and gave a single monomethiodide which was practically inactive against all the above organisms. An attempt to prepare an *N*-oxide of the parent (I; R = H) gave a mixture of the 4-hydroxy- and the 2 : 4-dihydroxy-derivatives; the structure of the latter, although most probable in view of similar results in the quinazoline series,[6] was not confirmed; an attempted unambiguous synthesis from the amino-acid (III; R = CO_2H, R′ = NH_2) and urea gave only the acid amide (III; R = $CO{\cdot}NH_2$, R′ = H).

Experimental

ω-Bromoacetophenone.—This was prepared in 60% yield by the method of Petrow *et al.*,[3] in batches: acetophenone (200 g.) and bromine (86 c.c., *not* 180 g. as in the reference quoted). Although the yield is much lower, this method is more convenient than that described in *Org. Synth., Coll. Vol. II*, p. 480.

2-Phenyl-3-phthalimidoquinoline-4-carboxylic Acid.—A solution of phenacylphthalimide (54 g.) in hot ethanol (200 c.c.), mixed with aqueous potassium hydroxide (40 g. in 40 c.c.), was added slowly with stirring to a solution of isatin (30 g.) in absolute ethanol (200 c.c.) containing potassium hydroxide (12 g. in 15 c.c. of water). Another aqueous solution of potassium hydroxide (25 g. in 50 c.c.) was added gradually and the solution was set aside for 3 days. The mixture was then almost neutralised with concentrated hydrochloric acid (approx. 28 c.c.), alcohol was distilled off under reduced pressure, water added, and the mixture acidified. The solid was collected, washed with water, and after digestion with hot 1% hydrochloric acid (1 l.) provided the acid (65 g.), m. p. 265—266° (decomp.), as an orange powder. Recrystallisation from dioxan yielded colourless crystals, m. p. 278° (decomp.).

3-Amino-2-phenylquinoline-4-carboxylic Acid.—100% Hydrazine hydrate (40 c.c.) and 2-phenyl-3-phthalimidoquinoline-4-carboxylic acid (80 g.) were heated under reflux in acetic acid (300 c.c.) for ½ hr. After 1 : 4-dihydroxyphthalazine (25 g.), m. p. *ca.* 340°, had been collected from the cold mixture, the filtrate was concentrated under reduced pressure to *ca.* 100 c.c. and set aside at 0°. The amino-acid (32 g.), m. p. 223—224°, separated and crystallised best from dioxan. The *acetyl derivative*, m. p. 271° (decomp.), was prepared under reflux by means of acetic anhydride containing a few drops of concentrated sulphuric acid (Found: C, 70·45; H, 4·7; N, 9·5. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·1%); Berlingozzi and Marzella [2] report m. p. 257—258° but give no analysis.

2-Phenyl-3-phthalimidoquinoline-4-carboxyamide.—The acid (105 g.) was heated under reflux with thionyl chloride (300 c.c.) for 15 min., excess of the reagent was removed under reduced pressure, and the granular solid was dissolved in benzene (1250 c.c.). A stream of dry ammonia was passed into this cold solution for 30 min., the solvent was removed, and the residue was washed with water and then alcohol, to yield the *amide* (75 g.), m. p. 325—330°; this separated from acetic acid in colourless needles, m. p. 343° (Found: C, 73·1; H, 3·9; N, 10·4. $C_{24}H_{15}O_3N_3$ requires C, 73·3; H, 3·8; N, 10·7%).

3-Amino-2-phenylquinoline-4-carboxyamide.—The foregoing amide (112 g., crude) was heated under reflux with 100% hydrazine hydrate (200 c.c.) and pyridine (400 c.c.) for 2 hr. The hot solution was poured into water (2 l.), and the white precipitate (66 g.), m. p. 265°, collected. Recrystallisation from methanol gave pale yellow needles, m. p. 265°, of the *amino-amide* (Found: C, 72·8; H, 5·0; N, 15·0. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 5·0; N, 16·0%). Use of acetic acid as solvent for this reaction gave a much reduced yield (>40%).

3-Amino-4-cyano-2-phenylquinoline.—An intimate mixture of the preceding compound (50 g.) and phosphoric oxide (125 g.) was heated at 175° for 1 hr. and then added to ice and water

[5] Albert and Royer, *J.*, 1949, 1148.
[6] Landquist, *J.*, 1956, 1885.

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(500 g. each) with stirring. The mixture was made alkaline with ammonia (*d* 0·880), to yield the *nitrile* (48 g.), m. p. 188—190°, which separated from benzene in pale yellow needles (31 g.), m. p. 194° (Found: C, 78·7; H, 5·0; N, 16·3. $C_{16}H_{11}N_3$ requires C, 78·35; H, 4·5; N, 17·1%).

4-Hydroxy-10-phenyl-1 : 3 : 9-triazaphenanthrene.—3-Amino-2-phenylquinoline-4-carboxylic acid (15 g.) was heated under reflux for 1 hr. with formamide (25 c.c.), and the product (8 g.) was collected from the cold mixture. The *hydroxy-derivative*, m. p. 307—308°, formed colourless needles from dioxan (Found: C, 74·3; H, 3·8; N, 15·1. $C_{17}H_{11}ON_3$ requires C, 74·7; H, 4·1; N, 15·4%).

4-Chloro-10-phenyl-1 : 3 : 9-triazaphenanthrene.—The pure 4-hydroxy-compound (7 g., recrystallised) and phosphorus pentachloride (11·5 g.) were heated at 150—160° for 22 hr. in a sealed tube. The cold product was removed with hot dry benzene (200 c.c.) and was shaken with ice (150 g.) and 6N-sodium hydroxide (100 c.c.) for 15 min.; the benzene layer was washed, dried (Na_2CO_3), and evaporated under reduced pressure. The *chloro-compound* (7·2 g.), m. p. 157°, crystallised from ethyl acetate or light petroleum (b. p. 80—100°) as needles, m. p. 167—168° (Found: C, 69·6; H, 3·5; N, 13·4; Cl, 10·85. $C_{17}H_{10}N_3Cl$ requires C, 69·9; H, 3·45; N, 14·4; Cl, 12·1%). The use of boiling phosphorus oxychloride, alone or with phosphorus pentachloride, did not give the desired product.

4-Amino-10-phenyl-1 : 3 : 9-triazaphenanthrene.—(*a*) A stream of dry ammonia was passed into a mixture of the chloro-compound (5 g.) and phenol (20 g.) for 1½ hr. at 180°. The mixture was heated on a steam-bath with 3N-sodium hydroxide (120 c.c.) for ½ hr., then filtered, and the precipitate washed with more sodium hydroxide solution and then copiously with water. The *amine* (4·6 g.) formed colourless blades, m. p. 233—234°, from benzene (Found: C, 75·3; H, 4·8; N, 19·8. $C_{17}H_{12}N_4$ requires C, 75·0; H, 4·4; N, 20·6%).

(*b*) 3-Amino-4-cyano-2-phenylquinoline (10 g.) and formamide (70 c.c.) were heated under reflux for 1 hr., then cooled, and the solid (9·5 g.) was collected and washed with water and then ethanol. Recrystallisation from ethyl acetate gave pale yellow platelets (3·15 g.), m. p. 233—234° identical with the authentic amine.

(*c*) The amine was also prepared in lower yield by heating the chloro-compound with urea in a sealed tube for 44 hr. at 190°.

(*d*) The 4-phenoxy-compound (50 mg.) was heated at 180° ± 10° with ammonium acetate (1 g.) for 30 min., dilute sodium hydroxide solution was added to the cold mixture, and the product was collected; recrystallisation from ethyl acetate gave the amine, m. p. and mixed m. p. 233°.

The *acetyl derivative*, m. p. 251—252°, prepared by boiling the amine with acetic anhydride for a few minutes, formed colourless needles from acetic acid (Found: C, 72·0; H, 4·4; N, 16·9. $C_{19}H_{14}ON_4$ requires C, 72·6; H, 4·5; N, 17·8%).

4-Amino-10-phenyl-1 : 3 : 9-triazaphenanthrene Methiodide.—The amine (2·5 g.) was heated under reflux with methyl iodide (25 c.c.) in methanol (25 c.c.) for 21 hr. The mixture was evaporated to dryness under reduced pressure and the *salt* (3·5 g.) crystallised from methanol or nitromethane as pale yellow needles, m. p. 239° (decomp.) (Found: C, 54·1; H, 3·6; N, 13·4; I, 28·2. $C_{18}H_{15}N_4I$ requires C, 52·2; H, 3·6; N, 13·5; I, 30·6%). Concentration of the mother-liquors yielded small clusters of dark red needles of another salt, m. p. 216° (decomp.), of which there was insufficient for analysis.

4-Phenoxy-10-phenyl-1 : 3 : 9-triazaphenanthrene.—The chloro-compound (1 g.) was heated in phenol (5 g.) containing potassium hydroxide (0·25 g.) on a steam-bath for 1½ hr., cooled, and shaken with 1·5N-sodium hydroxide (60 c.c.) for 30 min., and the product (1 g.) was collected. The *phenoxy-derivative*, m. p. 193—194°, formed colourless plates from benzene (Found: C, 78·9; H, 4·1; N, 10·2. $C_{23}H_{15}ON_3$ requires C, 79·1; H, 4·3; N, 12·0%).

10-Phenyl-1 : 3 : 9-triazaphenanthrene.—The chloro-compound (9·3 g.) was heated under reflux with toluene-*p*-sulphonhydrazide (11·6 g.) in dry chloroform (220 c.c.) for 2½ hr. The bright yellow intermediate (15·8 g.) was collected and added portionwise to N-sodium hydroxide (200 c.c.) on a steam-bath and left there for ½ hr. The crude *base* (7·5 g.) crystallised from methanol (charcoal) as colourless needles (4·2 g.), m. p. 173—175°, raised to 174—175·5° by recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 78·8; H, 4·5; N, 16·6. $C_{17}H_{11}N_3$ requires C, 79·4; H, 4·3; N, 16·3%).

The base (2·6 g.) was heated at 100° for 10 min. with dimethyl sulphate (15 c.c.). The mixture was dissolved in warm water (50 c.c.) and shaken with benzene (3 × 15 c.c.), and the aqueous layer was treated with a saturated solution of potassium iodide (15 c.c.); the cream

solid (3·6 g.), m. p. 207° (decomp.), was collected and washed successively with water, acetone, and ether. Recrystallisation from water gave yellow needles of a *monomethiodide*, m. p. 209° (decomp.) (Found: C, 52·8; H, 4·2; N, 9·85; I, 29·5. $C_{16}H_{16}ON_3I$ requires C, 51·9; H, 3·9; N, 10·1; I, 30·5%).

4-*Methyl*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene*.—4-Acetyl-3-amino-2-phenylquinoline (1 g.) was heated under reflux with formamide (10 c.c.) and acetic acid (7 c.c.) for 1 hr. and the crystalline product (0·35 g.) was collected. The *base* formed pale yellow needles, m. p. 157°, from ethyl acetate or light petroleum (b. p. 80—100°) (Found: C, 80·5; H, 4·9; N, 15·3. $C_{16}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%).

Reaction of Hydrogen Peroxide with 10-*Phenyl*-1 : 3 : 9-*triazaphenanthrene*.—The base (2·5 g.) was heated on a steam-bath for ¾ hr. with hydrogen peroxide (10 c.c., " 100-vol.") in acetic acid acid (20 c.c.), the mixture was cooled, and the product (2·3 g.), m. p. 295—299°, collected. Successive recrystallisation from acetic acid and dimethylformamide gave pale yellow needles of 4-hydroxy-10-phenyl-1 : 3 : 9-triazaphenanthrene, m. p. and mixed m. p. 305—306°.

The acetic acid mother-liquors and residues from recrystallisations (25 c.c. in all) were heated with hydrogen peroxide (200 c.c., " 100-vol.") at 75—80° for 2 hr., then cooled, and the pale yellow needles (0·8 g.), m. p. 324° (decomp.), were collected. This *substance* was identical with the compound, m. p. 330° (decomp.), prepared from the hydroxy-compound under the above conditions, which separated from dimethylformamide in colourless crystals (Found: C, 70·3; H, 3·85; N, 14·9. $C_{17}H_{11}O_2N_3$ requires C, 70·6; H, 3·8; N, 14·5%).

Reaction between 3-*Amino*-2-*phenylquinoline*-4-*carboxylic Acid and Urea*.—The amino-acid (1 g.) was heated at 160° ± 10° with urea (4 g.) for ½ hr., then warmed with water (20 c.c.) and acidified with concentrated hydrochloric acid (1 c.c.). A trace of solid, m. p. 360°, was collected and the filtrate was basified with aqueous ammonia to provide material (0·55 g.), m. p. 260—262° alone and when mixed with 3-amino-2-phenylquinoline-4-carboxyamide.

Methylation of 4-*Hydroxy*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene*.—A solution of the hydroxy-compound (1 g.) in 3N-sodium hydroxide (10 c.c.) was shaken at 60—70° with dimethyl sulphate (1 c.c.) for 15 min. and the product (0·7 g.) was collected and washed with dilute sodium hydroxide and then water. Recrystallisation from ethanol gave colourless needles, m. p. 174—175°, of 1(or 3)-*methyl*-4-*oxo*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene* (Found: C, 75·8; H, 4·6; N, 14·8. $C_{16}H_{13}ON_3$ requires C, 75·2; H, 4·6; N, 14·6%).

4-*Methoxy*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene*.—The 4-chloro-derivative (0·6 g.) and sodium methoxide [from sodium (0·25 g.) and methanol (15 c.c.)] were heated under reflux for 20 min.; the solution was evaporated to half-volume, cooled, and filtered. The solid was recrystallised from methanol and then from light petroleum (b. p. 80—100°) to yield colourless needles, m. p. 163°, of the *methoxy-compound* (Found: C, 75·4; H, 4·5; N, 14·7. $C_{16}H_{13}ON_3$ requires C, 75·2; H, 4·6; N, 14·6%).

We are indebted to the Medical Research Council for a grant for research assistance and to Dr. F. Hawking, of the National Institute for Medical Research, who arranged the biological tests.

CHEMISTRY DEPARTMENT, CHELSEA POLYTECHNIC. [*Received, March 19th*, 1957.]

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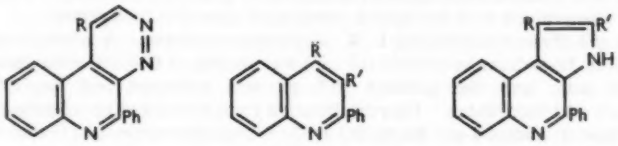
733. *Triazaphenanthrenes. Part II.* Derivatives of* 10-*Phenyl*-1 : 2 : 9-*triazaphenanthrene.*

By C. M. Atkinson and A. R. Mattocks.

A preparative route to 4-acetyl-3-amino-2-phenylquinoline has been developed. Diazotisation of the amino-ketone in hydrochloric acid and subsequent cyclisation gave mainly 4-acetyl-3-chloro-2-phenylquinoline, with 10% of the hydroxytriazaphenanthrene (I; R = OH); an 80% yield of the latter was obtained by cyclisation in an alkaline medium. 4-Amino-10-phenyl-1 : 2 : 9-triazaphenanthrene formed a monomethiodide which was biologically inactive.

Preparation of the amino-ketone (II; R = Ac, R′ = NH_2) for conversion into the triazaphenanthrene (I; R = OH) was unexpectedly difficult. No useful result was attained by condensation of ethyl 2-phenyl-3-phthalimidoquinoline-4-carboxylate (formed only *via* the acid chloride) with ethyl acetate (cf. ref. 1) and hydrolysis of the product. Likewise, reaction of the acid chloride with ethyl sodiomalonate gave a crystalline product in good yield, but hydrolysis to the amino-ketone could not be achieved. Heating the condensation product under reflux with 35% sulphuric acid gave 4-acetyl-2-phenyl-3-phthalimidoquinoline [II; R = Ac, R′ = $N(CO)_2C_6H_4$] and several variations in the strength of the acid or the duration of boiling yielded only the phthalimido-acid [II; R = CO_2H, R′ = $N(CO)_2C_6H_4$] or the amine (II; R = H, R′ = NH_2), the latter being also



(I) (II) (III)

formed by hydrolysis of the acetyl group from the phthalimido-ketone. Treatment of either the condensation product or the phthalimido-ketone with hydrazine in acetic acid yielded the hydrazone [II; R = $CMe{:}N{\cdot}NH_2$, R′ = $N(CO)_2C_6H_4$], but the free amine could not be obtained, nor was it possible to regenerate the ketone. An attempt to carry out a similar malonic ester synthesis starting from the amino-acid (II; R = CO_2H, R′ = NH_2) failed since the latter, on treatment with thionyl chloride under reflux, gave a sticky red solid which lost sulphur dioxide when kept and yielded 3-amino-4-chloro-2-phenylquinoline on digestion with cold hydrochloric acid. Similar treatment of 3-acetamido-2-phenylquinoline-4-carboxylic acid provided an unstable intermediate (containing sulphur and chlorine) which gave no useful product.

An alternative route to the amino-ketone involved oxidation of the condensed pyrrole (III; R = R′ = Me), but although this derivative was readily prepared *via* the hydrazine (II; R = H, R′ = $NH{\cdot}NH_2$), oxidation to a useful product with chromic acid or ozone was unsuccessful, as was the attempted oxidation of the compound (III; R = Me, R′ = Ph). These results were surprising in view of the beneficial effects of a *Bz*-nitro-group or a 2-phenyl group on the oxidation of indoles.[2]

The amino-ketone (II; R = Ac, R′ = NH_2) was eventually synthesised by a Grignard reaction with the amino-amide (II; R = $CO{\cdot}NH_2$, R′ = NH_2) or amino-nitrile, the intermediate ketimide being remarkably stable to cold hydrochloric acid but readily decomposed by hot acid or alkali or slowly by contact with alumina. Diazotisation of the amino-ketone in concentrated hydrochloric acid and subsequent heating, to cause ring-closure as in the

* Part I, preceding paper.

[1] Campbell, *J. Amer. Chem. Soc.*, 1946, **68**, 1837.
[2] Schofield, *J.*, 1950, 1505; Atkinson, Simpson, and Taylor, *J.*, 1954, 1381.

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Borsche reaction,[3] gave approximately 10% of the required 4-hydroxy-10-phenyl-1 : 2 : 9-triazaphenanthrene (I; R = OH) and 50% of 4-acetyl-3-chloro-2-phenylquinoline (II; R = Ac, R′ = Cl). However, diazotisation as before and ring-closure in a strongly alkaline medium at room temperature gave the desired product in 80% yield. This result was as unexpected as that obtained in concentrated acid, since the beneficial effect of the latter conditions has been emphasised by Schofield and Simpson.[3] These workers have stressed the importance of acid-catalysed enolisation of the ketone grouping as a prelude to ring closure, but in the present work such catalysis is largely nullified by salt formation at the ring nitrogen atom. It appears, therefore, that the mechanism of ring closure in this case is more correctly represented as an intramolecular coupling of the diazonium cation with the enolate anion,[4] the latter stabilised in an alkaline environment; experiments are in hand to test this hypothesis.

4-Hydroxy-10-phenyl-1 : 2 : 9-triazaphenanthrene (I; R = OH) readily yielded the chloro-compound (I; R = Cl) on treatment with phosphorus pentachloride and oxychloride under reflux, and the phenoxy-derivative (I; R = OPh) was obtained by standard methods. 4-Amino-10-phenyl-1 : 2 : 9-triazaphenanthrene (I; R = NH_2) formed a monomethiodide, but the site of quaternisation has not been determined. This salt was tested for biological activity by arrangement with Dr. F. Hawking, of the National Institute for Medical Research, and was found to be inactive against the organisms listed in the preceding paper.

As was expected, treatment of the hydroxy-compound (I; R = OH) with methyl sulphate yielded the *N*-methyl derivative, distinct from the *O*-methyl isomer prepared from the chloro-compound and sodium methoxide.

Experimental

3-Amino-2-phenylquinoline.—2-Phenyl-3-phthalimidoquinoline-4-carboxylic acid (40 g.) was heated under reflux with 50% v/v sulphuric acid (400 c.c.) for ½ hr. and the mixture was cooled, diluted to twice its volume, partially neutralised, and filtered (with filter-aid) to remove tar. The cold filtrate was basified with aqueous ammonia (*d* 0·880) and extracted three times with chloroform, to yield practically pure 3-amino-2-phenylquinoline (15 g.) as a pale yellow powder, m. p. not depressed on admixture with a sample, m. p. 119°, prepared by the method of Petrow *et al.*[5] Neutralisation of the mother-liquors and re-extraction with chloroform yielded the amino-acid (1 g.), m. p. and mixed m. p. 224°.

The amine was also formed by similar treatment of 2-phenyl-3-phthalimidoquinoline (see below).

The phthalimido-acid was recovered after 2 hours' heating with 20% or 75% sodium hydroxide solution.

2-Phenyl-3-phthalimidoquinoline.—The phthalimido-acid (2·5 g.) and phosphoric acid (15 c.c.; *d* 1·75) were heated at 215° ± 5° for 1 hr. Water (75 c.c.) was added and the pale yellow precipitate (2 g.) was collected and recrystallised repeatedly from benzene, to yield *2-phenyl-3-phthalimidoquinoline*, m. p. 249—250° (Found: C, 78·95; H, 4·25; N, 8·0. $C_{23}H_{14}O_2N_2$ requires C, 78·8; H, 4·0; N, 8·0%). Presence of 3-amino-2-phenylquinoline in the aqueous mother-liquor was indicated by its green fluorescence and by the sublimate of phthalic anhydride in the condenser.

3-Hydrazino-2-phenylquinoline Hydrochloride.—A solution of 3-amino-2-phenylquinoline (18 g.) in water (45 c.c.) and concentrated hydrochloric acid (75 c.c.) was diazotised at 0° with sodium nitrite (6 g. in 200 c.c. of water). The resultant solution was added at 0° to stannous chloride (54 g.) in concentrated hydrochloric acid (54 c.c.) and water (100 c.c.). The mixture was kept at 0° for ½ hr., allowed to reach room-temperature overnight, then diluted to 1500 c.c. and partially neutralised with sodium hydroxide solution (25 g. in 50 c.c.). Tin salts were removed as the sulphide, and the precipitate (collected with a filter-aid) was digested with boiling water (2 × 400 c.c.), the combined filtrates being concentrated to 350 c.c. and then

[3] Borsche and Herbert, *Annalen*, 1941, **546**, 293; Schofield and Simpson, *J.*, 1948, 1170.
[4] Leonard, *Chem. Rev.*, 1945, **37**, 269.
[5] Petrow, Stack, and Wragg, *J.*, 1943, 316.

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cooled in ice. The hydrazine hydrochloride (14·8 g.) separated as a yellow powder, m. p. 255° (decomp.).

The *hydrazone* of ethyl methyl ketone (16 c.c.) was prepared from this hydrochloride (10 g.) under reflux with sodium acetate (16 g.) in water (16 c.c.) and ethanol (25 c.c.) for 5 min. The derivative (9·3 g.) separated on cooling and formed light brown needles, m. p. 123°, from aqueous ethanol (Found: C, 78·9; H, 6·7; N, 14·8. $C_{19}H_{19}N_3$ requires C, 78·9; H, 6·6; N, 14·5%).

The derivative from propiophenone, prepared by the same method, was a sticky solid which could not be recrystallised.

4′ : 5′-Dimethyl-2-phenylpyrrolo(2′ : 3′-3 : 4)quinoline.—Ethyl methyl ketone 2-phenyl-3-quinolylhydrazone (9·3 g.) was heated on a steam-bath with concentrated hydrochloric acid (80 c.c.) for 6 hr. The precipitate (8·2 g.) was collected, washed with 50% hydrochloric acid, dissolved in the minimum volume of hot water, and recrystallised by cooling followed by the addition of concentrated hydrochloric acid, to give the pure *hydrochloride* (5·9 g.), m. p. ~300° (variable) (Found: C, 73·6; H, 5·7; N, 9·3; Cl, 10·0. $C_{19}H_{16}N_2$,HCl requires C, 73·9; H, 5·55; N, 9·1; Cl, 11·5%).

The *base*, m. p. 304—305°, obtained by making alkaline (ammonia) a solution of the hydrochloride, separated from benzene in colourless needles (Found: C, 83·8; H, 6·0; N, 10·5. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%). This compound was recovered unchanged after 4½ hours' heating with either acetyl chloride or acetic anhydride.

4′-Methyl-2 : 5′-diphenylpyrrolo(2′ : 3′-3 : 4)quinoline Hydrochloride.—Crude propiophenone 2-phenyl-3-quinolylhydrazone (2·8 g.) was heated on a steam-bath with concentrated hydrochloric acid (30 c.c.) for 6 hr. The precipitate was collected, washed with concentrated hydrochloric acid, and recrystallised three times from diluted hydrochloric acid and finally from water, to yield the *hydrochloride*, m. p. ~300° (variable) (Found: C, 73·2; H, 5·3; N, 7·2; Cl, 9·0. $C_{24}H_{18}N_2$,HCl,H_2O requires C, 74·2; H, 5·4; N, 7·2; Cl, 9·15%).

Ethyl 2-Phenyl-3-phthalimidoquinoline-4-carboxylate.—The acid (10 g.) was heated under reflux with thionyl chloride (30 c.c.) for ½ hr. and the cold mixture was treated with ethanol (50 c.c.) and then heated for a further ½ hr. Volatile products were removed under reduced pressure and the residue was recrystallised from ethanol, to provide colourless leaflets of the *ester*, m. p. 192—193° (Found: C, 73·3; H, 4·4; N, 6·9. $C_{26}H_{18}O_4N_2$ requires C, 73·9; H, 4·3; N, 6·6%).

4-Acetyl-2-phenyl-3-phthalimidoquinoline.—The acid (50 g.) was heated under reflux for ½ hr. with thionyl chloride (75 c.c.), the excess of thionyl chloride was removed under reduced pressure (finally with dry benzene), and the acid chloride was suspended in dry benzene (400 c.c.). This suspension was added to a hot stirred suspension of sodiomalonic ester prepared in the usual way from diethyl malonate (24 c.c.), powdered sodium (4·2 g.), and benzene (200 c.c.); the mixture was stirred for 18 hr., heated under reflux for 5 hr., stirred at room temperature for 18 hr., heated to *ca.* 60° and stirred for ½ hr. with diluted hydrochloric acid (60 c.c. of concentrated acid in 100 c.c. of water). The aqueous layer was extracted with benzene, and the original layer and combined extracts were washed, dried (Na_2SO_4), and evaporated to about 50 c.c. to yield crystals of the condensation product (*ca.* 35 g.), m. p. 184°. This substance (15 g.) was added to 35% v/v sulphuric acid (210 c.c.), and the suspension heated under reflux, with occasional shaking, for 10 min., cooled, and poured into water (300 c.c.). The solid (10 g.), m. p. 232°, furnished the pure *ketone*, m. p. 240—241°, on recrystallisation from ethanol (Found: C, 76·5; H, 4·2; N, 7·4. $C_{25}H_{16}O_3N_2$ requires C, 76·5; H, 4·1; N, 7·1%). The *oxime*, m. p. 240° (decomp.), separated from methanol as cream-coloured needles (Found: C, 72·6; H, 4·4; N, 10·0. $C_{25}H_{17}O_3N_3$ requires C, 73·7; H, 4·2; N, 10·3%).

On heating this ketone (3 g.) under reflux with acetic acid (20 c.c.) and 100% hydrazine hydrate (3 c.c.) for 4 hr. and recrystallising the product (2·3 g., m. p. 160—165°) from benzene–light petroleum (b. p. 60—80°) the *hydrazone* was obtained as an orange powder, m. p. 196° (decomp.) (Found: C, 73·6; H, 4·3; N, 13·2. $C_{25}H_{18}O_2N_4$ requires C, 73·9; H, 4·5; N, 13·8%).

When the ketone (0·5 g.) was heated under reflux with 48% hydrobromic acid (8 c.c.) for 3½ hr. and the solution was cooled, diluted, and filtered to remove a small amount of solid, basification of the filtrate yielded a pale yellow solid (0·25 g.) which crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 117—118° not depressed on admixture with 3-amino-2-phenylquinoline.

Action of Thionyl Chloride on 3-Amino-2-phenylquinoline-4-carboxylic Acid.—The amino-acid (2 g.) was heated under reflux for 30 min. with thionyl chloride (5 c.c.), the excess of thionyl

chloride removed under reduced pressure, and the red residue left at room temperature with 15% hydrochloric acid (20 c.c.) for a few hours and then filtered. The filtrate was made alkaline with aqueous ammonia, and the resultant sticky solid (1·5 g.) was dried and digested with boiling light petroleum (b. p. 80—100°); this provided *3-amino-4-chloro-2-phenylquinoline* (0·9 g.) as pale yellow needles, m. p. 126° (Found: C, 70·8; H, 4·6; N, 11·3; Cl, 12·6. $C_{15}H_{11}N_2Cl$ requires C, 70·7; H, 4·3; N, 11·0; Cl, 13·95%). The *acetyl derivative* formed colourless needles, m. p. 195°, from benzene (Found: C, 68·7; H, 4·4; N, 8·6; Cl, 11·6. $C_{17}H_{13}ON_2Cl$ requires C, 68·6; H, 4·4; N, 9·5; Cl, 11·95%). An identical experiment, in which the treatment with hydrochloric acid was omitted, yielded by digestion with light petroleum only a small quantity of an orange solid which became sticky on contact with air and spontaneously decomposed with evolution of sulphur dioxide. The compound, m. p. 126°, was unchanged after 2 hours' heating under reflux with 18% v/v sulphuric acid, but with 55% acid for 1 hr. gave a pale yellow solid, m. p. *ca.* 210°, on basification with aqueous ammonia. This provided, by recrystallisation from ethyl acetate–methanol, *3-amino-4-hydroxy-2-phenylquinoline*, m. p. 251° (decomp.) (Found: C, 75·9; H, 5·25; N, 12·1. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·1; N, 11·9%).

3-Amino-4-phenoxy-2-phenylquinoline.—A solution of 3-amino-4-chloro-2-phenylquinoline (0·5 g.) in phenol (*ca.* 7 g.) was treated with a stream of dry ammonia for 1·5 hr. at 195° ±15°. The cold mixture was treated with water (*ca.* 100 c.c.) and sodium hydroxide solution to dissolve phenol. Recrystallisation of the crude product from methanol gave pale yellow blades of the *phenoxy-compound* (0·3 g.), m. p. 175° (Found: C, 80·5; H, 5·4; N, 10·5. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·1; N, 9·0%). Treatment of the chloro-compound with phenol and potassium hydroxide at 100° failed to provide the phenoxy-compound. Attempts to convert this compound into the 4-amino-derivative, by heating in ammonium acetate at 140°, failed.

4-Acetyl-3-amino-2-phenylquinoline.—(*a*) 3-Amino-4-cyano-2-phenylquinoline (24 g.) was added during ½ hr. to a Grignard reagent prepared from magnesium (7·2 g.) and methyl iodide (20 c.c.) in ether (150 c.c.) and benzene (450 c.c.). The solution was heated under reflux for *ca.* 20 hr., cooled, and stirred with ice (1400 g.) and concentrated hydrochloric acid (360 c.c.) for 3½ hr. The organic layer was extracted with 5N-hydrochloric acid (2 × 150 c.c.) and the acid solution was then basified and extracted with benzene (3 × 300 c.c.). Evaporation of the washed and dried ($MgSO_4$) extract yielded a sticky solid which gave an almost pure product (22·4 g.; m. p. 130—133°) when washed with ether. The *ketimide*, m. p. 133—134°, formed almost colourless crystals from benzene–light petroleum (b. p. 80—100°) (Found: C, 77·8; H, 5·55; N, 15·1. $C_{17}H_{15}N_3$ requires C, 78·1; H, 5·8; N, 16·1%). The ketone (13·8 g.) was best prepared by heating the ketimide (15 g.) under reflux with water and concentrated hydrochloric acid (120 c.c.; 2 : 1 v/v) for 1 hr. For isolation, the reaction mixture was basified and extracted with ether, and the residue from evaporation of the washed and dried (Na_2SO_4) extract was recrystallised from *n*-hexane; the pure *ketone*, m. p. 93—94°, separated as pale yellow needles or blades (Found: C, 77·7; H, 5·3; N, 10·1. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%).

(*b*) 3-Amino-2-phenylquinoline-4-carboxyamide (35 g.) was added with stirring during 15 min. to a Grignard reagent prepared from magnesium (18 g.) and methyl iodide (54 c.c.) in ether (225 c.c.) and benzene (600 c.c.). The mixture was heated under reflux for 3½ hr., then cooled, and the ketimide (29 g.) was isolated as before and hydrolysed to give the almost pure ketone (25 g.).

Action of Nitrous Acid on 4-Acetyl-3-amino-2-phenylquinoline.—(*a*) A hot solution of the amino-ketone (12 g.) in concentrated hydrochloric acid (30 c.c.) and water (120 c.c.) was cooled to −5° and the finely divided suspension was treated below 0° with sodium nitrite (3·1 g.) in water (60 c.c.) during 5 min. The mixture was stirred below 0° and treated with 6N-sodium hydroxide (120 c.c.), then set aside at room temperature for 2 hr., filtered, and neutralised. The precipitate of *4-hydroxy-10-phenyl-1 : 2 : 9-triazaphenanthrene* (10·2 g.) formed plates, m. p. 262°, from ethanol (Found: C, 74·5; H, 4·0; N, 14·8. $C_{17}H_{11}ON_3$ requires C, 74·7; H, 4·1; N, 15·4%).

(*b*) The ketone (1 g.) was treated in concentrated hydrochloric acid (25 c.c.) at 0° with sodium nitrite (0·3 g.) in water (2 c.c.) during 5 min. After a few minutes, concentrated hydrochloric acid (75 c.c.) was added, and the mixture heated at 60° for 4 hr. Excess of acid was removed under reduced pressure and the residue neutralised with a concentrated solution of sodium acetate. The sticky solid (1 g.) was collected and recrystallised (charcoal) from ethanol, to provide crystals (0·6 g.), m. p. 98°; digestion with *n*-hexane gave an insoluble fraction (90 mg.; m. p. 253—255°) identical with the hydroxy-compound, m. p. 262°, and a soluble fraction,

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m. p. 100—101°, identified as *4-acetyl-3-chloro-2-phenylquinoline* (Found: C, 73·0; H, 4·6; N, 4·8; Cl, 12·0. $C_{17}H_{12}ONCl$ requires C, 72·5; H, 4·3; N, 5·0; Cl, 12·6%).

4-Chloro-10-phenyl-1 : 2 : 9-triazaphenanthrene.—The 4-hydroxy-compound (11 g.), phosphorus pentachloride (17 g.), and phosphoryl chloride (85 c.c.) were heated under reflux for 2½ hr. The phosphoryl chloride was distilled off under reduced pressure and the residue was shaken with benzene (100 c.c.), ice (150 g.), and 3N-sodium hydroxide (100 c.c.) for 20 min. The benzene layer, combined with further benzene extracts, was dried ($MgSO_4$) and evaporated to yield material (9·4 g.), m. p. 183°. The pure *chloro-compound*, m. p. 186°, separated as pale yellow blades from ethyl acetate (Found: C, 69·6; H, 3·35; N, 14·9; Cl, 12·5. $C_{17}H_{10}N_3Cl$ requires C, 69·9; H, 3·45; N, 14·4; Cl, 12·1%).

4-Phenoxy-10-phenyl-1 : 2 : 9-triazaphenanthrane.—(*a*) A stream of dry ammonia was passed through a solution of the foregoing chloro-compound (0·4 g.) in phenol (2 g.) at 180°. The stirred mixture was heated on a steam-bath with sodium hydroxide solution (4 g. in 30 c.c.) for 15 min., then cooled, and the product was collected and washed with 3N-sodium hydroxide, then with water. The product (0·4 g.; m. p. *ca.* 200°) crystallised from methyl acetate to provide pale pink needles of the *phenoxy-compound*, m. p. 221° (Found: C, 78·5; H, 3·9; N, 10·4. $C_{23}H_{15}ON_3$ requires C, 79·1; H, 4·3; N, 12·0%).

(*b*) The chloro-compound (6 g.) was heated on a steam-bath for 1½ hr. with potassium hydroxide (2 g.) in phenol (30 g.), the product cooled, and digested with warm 1·5N-sodium hydroxide (350 c.c.), and the phenoxy-compound (8 g.), m. p. and mixed m. p. 219—220°, was collected.

4-Amino-10-phenyl-1 : 2 : 9-triazaphenanthrene.—(*a*) The phenoxy-compound (1 g.) was heated in an open tube with ammonium acetate (*ca.* 10 g.) at 180—200° (bath) for 3 hr., the ammonium acetate being renewed as necessary. The cold mixture was digested with dilute sodium hydroxide solution, and the well-washed crude product (0·45 g.), m. p. *ca.* 255°, recrystallised from nitromethane to provide colourless needles, m. p. 276°, of the pure *amine* (Found: C, 74·9; H, 4·6; N, 18·15. $C_{17}H_{12}N_4$ requires C, 75·0; H, 4·4; N, 20·6%).

(*b*) A stream of dry ammonia was passed for ½ hr. into a solution of the phenoxy-compound (0·5 g.) in acetamide (5 g.) at 175° ± 5°. The mixture was cooled and diluted with water, and the product, m. p. *ca.* 210°, was collected and washed: this material could be separated into a portion (0·3 g.; m. p. 219—220°) insoluble in warm dilute hydrochloric acid and a soluble fraction (50 mg.; m. p. 269—270°) shown to be the phenoxy- and the amino-compound respectively.

4-Acetamido-10-phenyl-1 : 2 : 9-triazaphenanthrene.—The amine (0·09 g.) was heated under reflux with acetic anhydride (1·5 c.c.) for 5 min. and then for 15 min. on a steam-bath; the cold mixture was shaken with water and a little ethanol, and the product (90 mg.) was collected. Recrystallisation from acetic acid furnished the *acetyl derivative* as needles, m. p. 287—289° (Found: C, 71·0; H, 4·9; N, 17·7. $C_{18}H_{14}ON_4$ requires C, 71·5; H, 4·7; N, 18·5%).

4-Amino-10-phenyl-1 : 2 : 9-triazaphenanthrene Methiodide.—The amine (1·2 g., m. p. *ca.* 270°) was heated under reflux with methyl iodide (10 c.c.) in methanol (10 c.c.) for 2 hr., then cooled, and the product (1·5 g.) recrystallised from methanol, to give golden-yellow needles (0·9 g.) of the *salt*, m. p. 285° (decomp.) (Found: C, 52·15; H, 4·1; N, 13·3; I, 30·5. $C_{18}H_{15}N_4I$ requires C, 52·1; H, 3·65; N, 13·5; I, 30·7%).

N'-Methyl-4-oxo-10-phenyl-1 : 2 : 9-triazaphenanthrene.—A cold solution of the hydroxy-compound (1 g.) in 3N-sodium hydroxide (10 c.c.) was treated with dimethyl sulphate (1 c.c.), and the suspension was heated at *ca.* 55° for 5 min. The product (0·7 g.), m. p. 270°, was collected cold and recrystallised from ethyl alcohol and from *n*-butyl alcohol, to provide the *derivative*, m. p. 280—281°, as pale yellow leaflets (Found: C, 75·2; H, 4·4; N, 14·9. $C_{18}H_{13}ON_3$ requires C, 75·2; H, 4·6; N, 14·6%).

4-Methoxy-10-phenyl-1 : 2 : 9-triazaphenanthrene.—The 4-chloro-compound (0·6 g.) was heated under reflux for 2 hr. with methanolic sodium methoxide, prepared from sodium (0·25 g.) and methanol (15 c.c.). The mixture was evaporated to half-volume, then cooled, and the crystals (0·6 g.) were recrystallised from ethyl alcohol, to provide colourless needles of the *methoxy-compound*, m. p. 194—198° (Found: C, 75·3; H, 4·0; N, 14·6. $C_{18}H_{13}ON_3$ requires C, 75·2; H, 4·6; N, 14·6%).

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734. *Codehydrogenases. Part II.* A Synthesis of Nicotinamide Nucleotide.*

By L. J. Haynes, N. A. Hughes, G. W. Kenner, and Sir Alexander Todd.

The acyl groups can be satisfactorily removed from 3-*N*-(poly-*O*-acylglycosyl)carbamoylpyridinium halides with methanolic ammonia. Thus, nicotinamide nucleoside (I; R = H, Hal = Cl) has been synthesised from 1-acetyl-2 : 3 : 5-tri-*O*-benzoyl-D-ribose, and has been converted by means of phosphoryl chloride in methyl cyanide or nitromethane into nicotinamide nucleotide (II). Comparison of the synthetic nucleotide with that derived from cozymase shows that the former contains minor amounts of the isomeric nucleotide which has the α-configuration at the glycosidic carbon.

Nicotinamide nucleotide (II) has been produced from diphosphopyridine nucleotide (cozymase) by the action of a specific pyrophosphatase.[1] It is correspondingly a valuable starting material for the synthesis of diphosphopyridine nucleotide,[2] and we have therefore undertaken its synthesis from nicotinamide and D-ribose through the nucleoside (I; R = H).

The synthesis of a dihydro-derivative of the nucleoside (I; R = H) † was described in Part I,[3] but its great instability, particularly towards acid, rendered it an unsuitable starting point for further elaboration of the nucleotide structure. This dihydro-derivative had been prepared from the triacetyl quaternary riboside bromide (I; R = Ac, Hal = Br) by reduction with sodium dithionite and subsequent deacetylation with methanolic ammonia. Hitherto ammoniacal deacylation of the quaternary glycosides themselves has been regarded as prohibited by their notorious instability under alkaline conditions. Consequently acidic hydrolysis has been employed and, when most of our work had been completed, the application of this method to the acetylated ribofuranoside was described.[4] However, in our experience, there is also considerable hydrolysis of the glycosidic link, particularly with the ribofuranoside. Therefore our observation that ammoniacal deacetylation can indeed be applied satisfactorily to quaternary glycosides, provided that care is taken, has been of the utmost assistance to us. By this means the quaternary glucopyranoside of nicotinamide has been obtained crystalline for the first time, and the preparation of the ribofuranoside is also satisfactory.

For the routine preparation of nicotinamide nucleoside (I; R = H) some improvements in our earlier condensation method [3] were made. Tri-*O*-acetylribofuranosyl chloride has been preferred to the bromide as a reagent for the synthesis of purine nucleosides,[5] and it has proved superior in the present work. The acetylated nucleoside chloride (I; R = Ac, Hal = Cl) was obtained crystalline and in better yield than the amorphous bromide. Meanwhile Fletcher and his colleagues showed that 1-*O*-acetyl-2 : 3 : 5-tri-*O*-benzoyl-D-ribose can be obtained from ribose through methyl ribofuranoside in one series of operations.[6] Therefore we adopted this beautifully crystalline substance as our starting material in preference to 1 : 2 : 3 : 5-tetra-*O*-acetyl-D-ribose,[7] although, as described in the Experimental section, the latter can indeed be prepared in a similar fashion but lower yield. The benzoylated nucleoside (I; R = Bz, Hal = Cl) was obtained in good yield

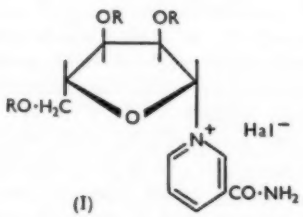
* Part I, *J.*, 1950, 303.

† The majority, if not all, of the synthetic materials described here are mixtures of β- and α-anomers, but generally the β-form (as shown in the structural formulæ) predominates. This point is discussed later in the text.

[1] Kornberg and Pricer, *J. Biol. Chem.*, 1950, **186**, 557.
[2] Hughes, Kenner, and Todd, following paper.
[3] Haynes and Todd, *J.*, 1950, 303.
[4] Viscontini, Marti, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1373.
[5] Davoll, Lythgoe, and Todd, *J.*, 1948, 967.
[6] Ness, Diehl, and Fletcher, *J. Amer. Chem. Soc.*, 1954, **76**, 763.

from the chloro-sugar in either methyl cyanide or, slightly better, nitromethane solution, but it could not be crystallised. The benzoyl groups were removed by methanolic ammonia without difficulty.

The nicotinamide nucleoside (I; R = H, Hal = Cl) prepared through either the acetylated or the benzoylated intermediate was a hygroscopic amorphous powder with the correct elementary composition. Its furanoside nature followed from its mode of synthesis and from its consumption of scarcely more than 1 mol. of periodate during 20 hr. at 0°. Viscontini, Marti, and Karrer [4] concluded that a nucleoside prepared from 1 : 2 : 3 : 5-tetra-*O*-acetyl-D-ribose in a different way [4] had a pyranose structure because it consumed 2 mols. of periodate during several days at room temperature. However, we have found that quaternary nicotinamide derivatives, such as *N*-benzyl-3-carbamoylpyridinium chloride and 3-*N*-(2′ : 3′ : 4′ : 6′-tetra-*O*-acetyl-D-glucopyranosyl)carbamoylpyridinium bromide, but not nicotinamide itself, are oxidised by periodate at room temperature, while they are stable at 0°. The evident need to work at the lower temperature recalls the similar case of riboflavin derivatives.[8] A later examination [9] of the initial oxidation product by reduction, hydrolysis, and paper chromatography convinced the Swiss workers that their material was actually furanoside.



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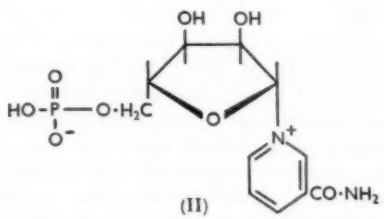


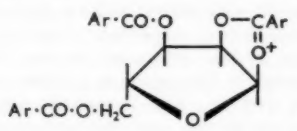
(II)

A much more difficult question is whether the synthetic and the natural nucleoside have the same configuration at the glycosidic centre. Unfortunately the optical rotation of the nucleoside obtained by enzymic degradation of cozymase [10] has not been recorded. The synthetic nucleotide (II) has $[\alpha]_D$ −38° (in H_2O) while the anomer, obtained in an ingenious way from an impurity in some samples of cozymase, has $[\alpha]_D$ +58°.[11] These values support the customary assumption that cozymase is a derivative of β-D-ribofuranose (cf. formulæ I and II), and it may be reasonably supposed that the anomeric nucleosides have rotations similar to those of the nucleotides. These considerations encouraged us to believe that our synthetic nucleoside, having $[\alpha]_D$ −28°, consisted at any rate mainly of the natural β-anomer. Recently a contrary view has been taken, for Viscontini and Hürzeler-Jucker [12] have deduced from the velocities of periodate oxidation of various nicotinamide nucleosides that the ribofuranoside [4] having $[\alpha]_D$ +49° is the β-anomer. Their conformational arguments appear to have several defects, which it would be out of place to examine here. We prefer to attach the usual significance to the sign of rotation even though there are considerable variations among the glycosylamines due to their differing light absorptions.[13] We recall that, for example, the anomeric ribofuranosides of 5 : 6-dimethylbenziminazole obey the rule (α- having $[\alpha]_D$ +14°, β- $[\alpha]_D$ −44°),[14,15] and that their configurations are assured by the *X*-ray analysis [16] of vitamin B_{12}. If we are wrong,

[7] Howard, Lythgoe, and Todd, *J.*, 1947, 1052.
[8] Forrest and Todd, *J.*, 1950, 3295.
[9] Viscontini, Hoch, Marti, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 646.
[10] Schlenk, *Arch. Biochem.*, 1943, **3**, 93.
[11] Kaplan, Ciotti, Stolzenbach, and Bachur, *J. Amer. Chem. Soc.*, 1955, **77**, 815.
[12] Viscontini and Hürzeler-Jucker, *Helv. Chim. Acta*, 1956, **39**, 1620.
[13] Cf. Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 861.
[14] Holly, Shunk, Peel, Cahill, Lavigne, and Folkers, *J. Amer. Chem. Soc.*, 1952, **74**, 4521.
[15] Johnson, Miller, Mills, and Todd, *J.*, 1953, 3061.
[16] Hodgkin *et al.*, *Proc. Roy. Soc.*, 1957, *A*, in the press.

then cozymase is an α-glycoside in the nicotinamide moiety because our synthetic nucleoside has been correlated with it, first through phosphorylation to the nucleotide (II) and, secondly, through synthesis of cozymase itself.[2]

Phosphorylation of the nucleoside presented difficulties. It was insoluble in organic solvents and sufficiently unstable to render improbable schemes for protection of the 2′- and 3′-hydroxyl groups with, say, an *iso*propylidene residue. Therefore, in collaboration with Dr. R. L. Hinman, we explored direct routes to nucleosides from ribose derivatives already carrying at the 5′-position a reactive group, such as iodo, or even a protected phosphoryl residue. The results were in general disappointing and we turned to the æsthetically less satisfying direct phosphorylation of the nucleoside. Some preliminary experiments with phosphoryl chloride in moist pyridine, a reagent used successfully in the riboflavin field,[3] were encouraging, but the nucleoside had a half-life of only 18 hr. in pyridine at room temperature, being converted into another glycoside, identified with quaternary pyridine ribofuranoside by paper chromatography (*i.e.*, there had been an exchange of nicotinamide and pyridine). The corresponding reaction with 2 : 6-lutidine was much slower, but lutidine reacted with phosphoryl chloride forming a yellow precipitate. The nucleoside however was stable when dissolved in anhydrous *m*-cresol or dimethylformamide or when suspended in methyl cyanide or nitromethane. The last provided the best medium for phosphorylation, although methyl cyanide was almost as good; about 20% of the nucleoside was phosphorylated during four days with phosphoryl chloride at room temperature. The nucleotide fraction was isolated by passage through cation- and anion-exchange resins. It was retained by the latter sufficiently long to effect separation from ribose, but a more efficient technique, cation-exchange chromatography in formic acid solution,[2] was discovered after completion of this work. Fortunately the only nucleotide produced was the 5′-phosphate (II), so far as could be detected by our methods of analysis, *viz.*, treatment with snake-venom 5′-nucleotidase (which caused complete breakdown to



(III)

nucleoside), periodate titration, and both chromatography and electrophoresis on paper in presence of borate ions. Moreover, the paper chromatographic behaviour of the synthetic nucleotide was identical with that of a sample of the degradation product of natural cozymase, generously supplied by Dr. A. Kornberg of the National Institutes of Health, Bethesda.

The optical rotation (−24°) of our synthetic nucleotide corresponded to the presence of β- and α-anomers in 4 : 1 ratio, and this composition was confirmed by the further synthetic experiments described in the following paper.[2] As no satisfactory technique for separating the anomers was available, we considered the possibility of steering the nucleoside synthesis towards the β-anomer. It seemed possible that formation of the latter could arise through nucleophilic attack on the cation (III); if so then an increase in neighbouring-group participation might well offer a solution of the problem. Accordingly the synthesis was repeated with *p*-anisoyl instead of benzoyl residues, and indeed the nucleoside obtained had $[\alpha]_D$ −36° instead of the previous −28°. However, this result was not consistently reproduced and in fact there appeared to be little advantage, apart from the crystallinity of methyl 2 : 3 : 5-tri-*O*-*p*-anisoyl-D-ribofuranoside, in working with anisoyl derivatives. Lack of consistency in the proportions of anomers was also encountered in the benzoyl series. Bearing in mind the aglycone-interchange reaction observed when the nucleoside is dissolved in pyridine (see above), we examined the course of the quaternisation polarimetrically. The optical rotation fell steadily, but it never became negative despite the negative rotation of the isolated product. It may be noted

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that the acetylated amorphous nucleoside of Viscontini, Marti, and Karrer [4] had $[\alpha]_D$ +43°, although our crystalline material (I; R = Ac, Hal = Cl) had $[\alpha]_D$ −59°; the chief apparent difference between the preparations was that the Swiss workers used the bromo- instead of the chloro-sugar and there was acetic acid in their reaction medium. At present the factors controlling the proportions of anomers are regrettably obscure.

Experimental

All analytical samples were dried at 20°/10^{-3} mm.

3-(N-β-D-*Glucopyranosylcarbamoyl*)*pyridinium Bromide*.—The crystalline acetylated glucoside [17,3] (20 g.) was dissolved in boiling methanol (500 c.c.), and the solution cooled to 0°, saturated with ammonia gas, and then kept overnight at 0°. The orange solution was then concentrated to 80 c.c. under reduced pressure and set aside. Next day the microcrystalline solid (12 g., 88%) was collected. The colourless *glucoside* (60%), m. p. 157—158° (decomp.), was obtained by charcoal-treatment of an aqueous solution, which was evaporated twice with ethanol; the residue crystallised from hot methanol although the recrystallised material was very sparingly soluble in this solvent. The glucoside had $[\alpha]_D^{18}$ +32·2° (*c* 1·8 in H_2O) and $\varepsilon_{max.}$ 5060 at 265 mμ (Found: C, 40·0; H, 5·1; N, 7·5. $C_{12}H_{17}O_6N_2Br$ requires C, 39·5; H, 4·7; N, 7·7%).

1 : 2 : 3 : 5-*Tetra*-O-*acetyl*-D-*ribose*.—A solution of D-ribose (5 g., dried at 1 mm.) in dry methanol (120 c.c.), containing 1% of hydrogen chloride, was kept for 45 min. at 20° before addition of dry pyridine (6 c.c.). The solvents were then evaporated, finally at 1 mm. The residual syrup was dissolved in dry pyridine (80 c.c.), which was cooled to 0° and treated with acetic anhydride (25 c.c.). The mixture was kept overnight at room temperature and it was then stirred with ice-water for 1 hr. The neutral product was isolated by the usual chloroform-extraction and evaporation. A 50% w/v solution (20 c.c.) of hydrogen bromide in acetic acid was added to a solution of the resulting syrup in acetic acid. After being kept for 45 min. at room temperature the mixture was treated with chloroform (200 c.c.) and ice (200 g.). The chloroform extract was washed at 0° with water, sodium hydrogen carbonate solution, and again water before being run into a stirred suspension of silver carbonate (5 g.) in acetone (90 c.c.) and water (2 c.c.). After 30 min. the solution was filtered and evaporated. The residue was thoroughly dried by two-fold dissolution in pyridine and evaporation, before being kept overnight with dry pyridine (40 c.c.) and acetic anhydride (10 c.c.). The resulting solution was stirred with ice-water for 30 min. and the neutral product isolated by the usual chloroform-extraction. Recrystallisation from ethanol afforded 1 : 2 : 3 :5-tetra-*O*-acetyl-D-ribose, m. p. and mixed m. p. 82°, $[\alpha]_D^{20}$ −12·4° (*c* 4·5 in $CHCl_3$), in agreement with the literature [18] (yield: 2·0 g., 19%).

3-N-(2′ : 3′ : 5′-*Tri*-O-*acetyl*-D-*ribofuranosyl*)*carbamoylpyridinium Chloride*.—A solution of acetochlororibofuranose [5] (from 5 g. of 1 : 2 : 3 : 5-tetra-*O*-acetyl-D-ribose) in methyl cyanide (50 c.c., freshly distilled from phosphoric oxide) was added to a solution of nicotinamide (2·5 g., dried overnight at 120°) in methyl cyanide (400 c.c.) at 0°. A colourless precipitate of nicotinamide hydrochloride started to separate in 10 min., and the mixture was set aside at 0° for 42 hr. The solution was evaporated and chloroform (25 c.c.) added. Next day the precipitate was removed and washed with chloroform (15 c.c.), and the combined filtrate and washings were concentrated to 25 c.c. Rapid addition of dry ether (150 c.c.) gave a fine white precipitate which coagulated when shaken. The liquors were decanted and the precipitate was washed by decantation with dry ether. Nicotinamide was extracted with ethyl acetate from the solid, which was evaporated several times with methanol or chloroform. The residue, which originally gave an emulsion with chloroform, could then be dissolved in that solvent (40 c.c.). Dry ethyl acetate was added cautiously to the pale yellow solution until a sticky precipitate started to appear on the walls of the vessel. There ensued a rapid crystallisation of the colourless acetylated *nucleoside* (2·35 g., 62%), $[\alpha]_D^{18}$ −58·7° (*c* 1·6 in H_2O) (Found: C, 48·6; H, 5·4; N, 6·8. $C_{17}H_{21}O_8N_2Cl$ requires C, 49·0; H, 5·1; N, 6·7%).

3-N-(2′ : 3′ : 5′-*Tri*-O-*benzoyl*-D-*ribofuranosyl*)*carbamoylpyridinium Chloride*.—1-*O*-Acetyl-2 : 3 : 5-tri-*O*-benzoyl-D-ribose, m. p. 130—131°, $[\alpha]_D^{20}$ +44·0° (*c* 1·5 in $CHCl_3$), was prepared

[17] Karrer, Ringier, Büchi, Fritzsche, and Solmssen, *Helv. Chim. Acta*, 1937, **20**, 55.
[18] Zinner, *Chem. Ber.*, 1950, **83**, 153.

essentially according to Kissmann *et al.*[19] The 1-chloro-derivative, $[\alpha]_D^{20}$ +69·7° (*c* 1·9 in nitromethane), was prepared from 8·3 g. in the usual way [5] and dissolved in either nitromethane or methyl cyanide (80 c.c.). This solution was added to a cold solution of nicotinamide (2·8 g.) in the same solvent (200 c.c.). The mixture was kept at 0° for 36 hr. before the nicotinamide hydrochloride was filtered off. Evaporation yielded a foam which was dissolved in ether (100 c.c.) and water (100 c.c.). The aqueous layer was washed with ether (2 × 50 c.c.) and then extracted with chloroform (2 × 50 c.c.). The chloroform extracts were dried (Na_2SO_4) and concentrated to small bulk (20 c.c.). Dropwise addition of this solution (20 c.c.) to dry ether (300 c.c.) precipitated the amorphous benzoylated *nucleoside* (4·0 g., 40%), $[\alpha]_D^{20}$ −44·0° (*c* 3·4 in MeOH) (Found: C, 62·6; H, 4·8; N, 4·7. $C_{32}H_{27}O_8N_3Cl,\frac{1}{2}H_2O$ requires C, 62·8; H, 4·6; N, 4·6%). It was advisable to allow the precipitate to age for several hours before attempting filtration.

3-(N-D-*Ribofuranosylcarbamoyl*)*pyridinium Chloride* (*Nicotinamide Nucleoside*).—(a) *From the benzoyl derivative.* A solution of the foregoing compound (2·0 g.) in dry methanol (200 c.c.) was saturated at 0° with dry ammonia and then set aside at 0° for 18 hr. The yellow gum left on evaporation was dissolved in dry methanol (10 c.c.) and added to dry ethyl acetate (500 c.c.). The flocculent precipitate was collected by centrifugation, dissolved in methanol, and reprecipitated. The *nucleoside* (0·71 g., 73%) was obtained as a very hygroscopic, yellow, amorphous powder, $[\alpha]_D^{20}$ −28·6° (*c* 2·78 in MeOH), consuming 1·14 mols. of periodate during 14 hr. at 0° (Found: C, 43·9; H, 6·2; N, 9·5. $C_{11}H_{15}O_5N_2Cl,\frac{1}{2}H_2O$ requires C, 44·1; H, 5·4; N, 9·4%).

(b) *From the acetyl derivative.* The crystalline 3-*N*-(2′ : 3′ : 5′-tri-*O*-acetyl-D-ribofuranosyl)-carbamoylpyridinium chloride was deacetylated in the same way (Found: C, 44·0; H, 5·9; N, 9·2%).

Nicotinamide Nucleotide.—A suspension of 3-*N*-D-ribofuranosylcarbamoylpyridinium chloride (nicotinamide nucleoside) (7·44 g., dried to constant weight at 20°/1 mm.) in dry nitromethane (400 c.c.) was shaken vigorously for 12 hr. To this fine suspension was added water (1 c.c.), followed by phosphoryl chloride (11 c.c., freshly distilled). The mixture was shaken vigorously with exclusion of moisture at 20° during 4 days. The solution was then concentrated to 30 c.c. and diluted with ice-water (500 c.c.). The pH was adjusted to 5·0 with 10% aqueous ammonia, and the solution was concentrated to 250 c.c. before being passed through a column (30 cm. × 20 cm.²) of Dowex-2 anion-exchange resin (acetate form). The column was washed with 0·001N-acetic acid (300 c.c.) to remove the last traces of nucleotide. The combined filtrate and washings, which were free from phosphate and chloride ions, were concentrated to 250 c.c. before being passed through a column (30 cm. × 20 cm.²) of Dowex-50 cation-exchange resin (hydrogen form). The last traces of nucleotide were washed through with water (300 c.c.), and the combined solutions, which were free from nicotinamide and nicotinamide nucleoside, were concentrated to 20 c.c. and freeze-dried. The resulting gummy solid (1·3 g.) contained about 90% of nicotinamide nucleotide, most of the remainder being water; it was used directly for further stages of synthesis.[2]

A solution of this material (0·1 g.) in water (2 c.c.) was brought to pH 7 by addition of ammonia solution and then added to a column (15 cm. × 10 cm.²) of Dowex-2 resin (acetate form). The column was washed with water (1 c.c. per min.), which was collected in 10 c.c. fractions. Generally the first ten tubes contained a little nicotinamide and ribose, and then the nucleotide (detected by absorption at 266 mμ) was eluted in the next ten; sometimes 0·001N-acetic acid was needed to elute the nucleotide at a reasonable rate. The *nicotinamide nucleotide* was recovered by concentration and freeze-drying as a colourless amorphous hygroscopic solid with $[\alpha]_D^{20}$ −24° (*c* 2·0 in water) (Found: C, 36·0; H, 4·5; N, 7·7; P, 8·35. $C_{11}H_{15}O_8N_2P,2H_2O$ requires C, 35·6; H, 5·1; N, 7·6; P, 8·4%). It consumed 1·1 mols. of periodate during 14 hr. at 0°. A mixture of the nucleotide (1 mg.), 0·25M-glycine buffer of pH 8·5 (0·3 c.c.), 0·1M-magnesium chloride (0·1 c.c.), and a solution of *Crotalus atrox* venom (2 mg.) in 0·1M-potassium chloride (0·1 c.c.) was incubated at 37° for 4 hr.; paper chromatography then revealed complete hydrolysis of the nucleotide to nucleoside and inorganic phosphate.

Paper Chromatography.—The nicotinamide derivatives were detected by viewing or photographing the chromatograms in the light of a mercury lamp. Quaternary pyridinium derivatives could also be detected [20] by fuming the paper with ammonia and ethyl methyl ketone for 30 min., which produced fluorescent spots. Ascending chromatography on Whatman No. 1

[19] Kissmann, Pidacks, and Baker, *J. Amer. Chem. Soc.*, 1955, **77**, 18.
[20] Kodicek and Reddi, *Nature*, 1951, **168**, 475.

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paper was carried out with butan-1-ol–acetic acid–water in the ratios either 5 : 2 : 3 (system A) or 20 : 3 : 7 (system B). R_P values were (given first for system A): ribose 0·40, 0·27; nicotinamide 0·67, 0·65; nicotinamide nucleoside chloride 0·28, 0·15; *N*-D-ribofuranosylpyridinium chloride 0·47, 0·36; 2 : 6-dimethyl-*N*-D-ribofuranosylpyridinium chloride 0·58, 0·41; nicotinamide nucleotide 0·18, 0·05; inorganic phosphate 0·30 (in A). The benzoyl and *p*-anisoyl derivatives of the nucleoside both had R_P 0·83 in system B. The comparison of the synthetic nucleotide with Dr. Kornberg's sample was also made by descending chromatography during 5 days in propan-2-ol (100 c.c.)–water (50 c.c.)–boric acid (0·5 g.)–ammonia (to pH 9); R_P values were very small.

Methyl 2 : 3 : 5-*Tri*-O-p-*anisoyl*-D-*ribofuranoside*.—A solution of D-ribose (6 g., dried at 20°/1 mm.) in dry methanol (120 c.c.), containing 1% of hydrogen chloride, was kept for 45 min. at 20° before the addition of dry pyridine (6 c.c.). The solvents were evaporated, finally at 1 mm., and the residual syrup was taken up in dry pyridine (75 c.c.). *p*-Anisoyl chloride (32 g.) was added slowly to the stirred solution at 0°. A precipitate of pyridine hydrochloride was formed almost immediately. The solution was kept overnight at room temperature and then poured into ice-water (4 l.). The usual chloroform extraction yielded a neutral product, which crystallised from methanol in needles. Recrystallisation afforded *methyl* 2 : 3 : 5-*tri*-O-p-*anisoyl*-D-*ribofuranoside* (12·5 g., 55%), m. p. 86—88°, $[\alpha]_D^{20}$ +109·5° (*c* 2·0 in $CHCl_3$) (Found, in material dried at 60°: C, 63·6; H, 5·2. $C_{30}H_{30}O_{11}$ requires C, 63·7; H, 5·3%).

1-O-*Acetyl*-2 : 3 : 5-*tri*-O-p-*anisoyl*-D-*ribofuranose*.—The liquors, from which the foregoing substance had been crystallised, were evaporated, finally at 1 mm. The resulting syrup was dissolved in acetic acid (16 c.c.) and treated at 20° with a 50% w/v solution (1 c.c.) of hydrogen bromide in acetic acid. After 20 min. the precipitate of anisic acid was filtered off and the filtrate was diluted with acetic acid (100 c.c.). Water (25 c.c.) was added gradually to the ice-cooled solution, and the neutral product was then isolated by the customary treatment with ice-water and chloroform-extraction. Crystallisation and recrystallisation from ethanol afforded colourless needles of 1-O-*acetyl*-2 : 3 : 5-*tri*-O-p-*anisoyl*-D-*ribofuranose* (3·0 g., 13%), m. p. 123—125°, $[\alpha]_D^{20}$ +84·4° (*c* 2·0 in $CHCl_3$) (Found, in material dried at 70°: C, 62·4; H, 5·0. $C_{31}H_{30}O_{12}$ requires C, 62·6; H, 5·1%). From the liquors there were obtained, by acetylation with acetic anhydride in pyridine and the usual isolation procedure, a further 2·0 g. (9%) of the same compound and another more soluble substance (0·65 g., 3%), m. p. 117—119°, $[\alpha]_D^{20}$ +80·5° (*c* 0·75 in $CHCl_3$) (Found, in material dried at 60°: C, 62·9; H, 5·3%). This substance, which had a very similar infrared spectrum to 1-*O*-acetyl-2 : 3 : 5-tri-*O*-*p*-anisoyl-D-ribofuranose, was probably 2-*O*-acetyl-1 : 3 : 5-tri-*O*-*p*-anisoyl-D-ribofuranose; treatment of it with hydrogen bromide in acetic acid liberated almost 1 mol. of anisic acid.

3-(N-2′ : 3′ : 5′-*Tri*-O-p-*anisoyl*-D-*ribofuranosyl*)*carbamoylpyridinium Chloride*.—Either methyl 2 : 3 : 5-tri-*O*-*p*-anisoyl-D-riboside or the corresponding 1-acetate was converted into the 1-chloro-derivative and brought into reaction with nicotinamide, in the same way as 1-*O*-acetyl-2 : 3 : 5-tri-*O*-benzoyl-D-ribose. The anisoylated *nucleoside* (27%) was obtained as a colourless amorphous powder, $[\alpha]_D^{20}$ −38·4° (*c* 2·5 in MeOH) (Found, in material dried at 50°: C, 60·6; H, 4·8; N, 4·0. $C_{35}H_{33}O_{11}N_2Cl$ requires C, 61·1; H, 4·8; N, 4·0%). Nicotinamide nucleoside chloride with $[\alpha]_D^{20}$ −36° (*c* 2·3 in MeOH) was obtained in 40% yield by the standard ammoniacal deacylation.

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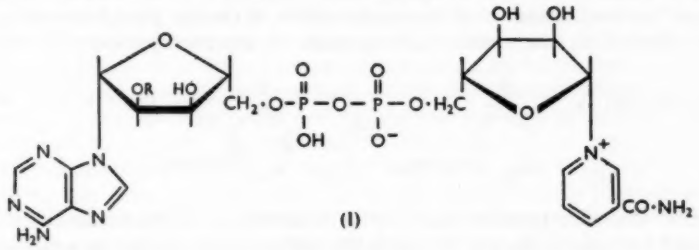
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 28th*, 1957.]

735. *Codehydrogenases. Part III.* A Synthesis of Diphosphopyridine Nucleotide (Cozymase), and Some Observations on the Synthesis of Triphosphopyridine Nucleotide.*

By N. A. Hughes, G. W. Kenner, and Sir Alexander Todd.

Condensation of nicotinamide nucleotide [1] and adenosine-5′ phosphate, dissolved in aqueous pyridine, has been accomplished by adding a large excess of di*cyclo*hexylcarbodi-imide. Only a small amount of the nicotinamide nucleotide is converted into the symmetrical pyrophosphate, and some 50% of it condenses to yield diphosphopyridine nucleotide, which can be separated by ion-exchange chromatography. This coenzyme fraction, like the nicotinamide nucleotide used in its preparation, is a mixture of α- and β-forms. The pure β-form has been isolated by reduction with alcohol and alcohol dehydrogenase, alkaline destruction of the unreduced α-isomer, and enzymic regeneration from the dihydro-form. Preliminary experiments on the condensation of nicotinamide nucleotide with a mixture of adenosine-2′ : 5′ and -3′ : 5′ diphosphate [2] have given a product containing triphosphopyridine nucleotide (TPN), which has been obtained by ion-exchange chromatography as a mixture of isomers.†

Although diphosphopyridine nucleotide (cozymase, DPN, coenzyme I, codehydrogenase I) (I; R = H) [4,5] is the longest-known coenzyme, comparatively little progress towards its synthesis has been hitherto recorded. While the present study was under way, it was reported [6] that this coenzyme can be detected enzymically in the mixture produced from nicotinamide nucleotide (derived from natural sources) and adenosine-5′ phosphate



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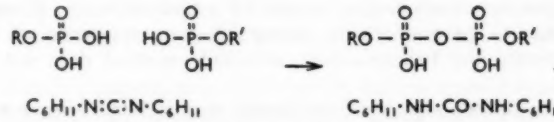

by the action of trifluoroacetic anhydride.[7] Having developed a relatively convenient synthesis of nicotinamide nucleotide,[1] we were in a position to examine thoroughly this type of condensation, which forms the final step in the scheme of synthesis envisaged in Part I.[8] Various methods of condensation have been used successfully by us in the

* Part II, preceding paper.

† A preliminary announcement of these results was made in a lecture given to the Basle Chemical Society in July 1955 which has since been published.[3]

[1] Haynes, Hughes, Kenner, and Todd, preceding paper.
[2] Cramer, Kenner, Hughes, and Todd, *J.*, 1957, 3297.
[3] Todd, *Stoll Festschrift*, Birkhauser, Basle, 1957, p. 508.
[4] Lythgoe, *Ann. Reports*, 1945, **42**, 180.
[5] Singer and Kearney, *Adv. Enzymol.*, 1954, **15**, 79.
[6] Shuster, Kaplan, and Stolzenbach, *J. Biol. Chem.*, 1955, **215**, 195.
[7] Cf. Christie, Elmore, Kenner, Todd, and Weymouth, *J.*, 1953, 2947.
[8] Haynes and Todd, *J.*, 1950, 303.

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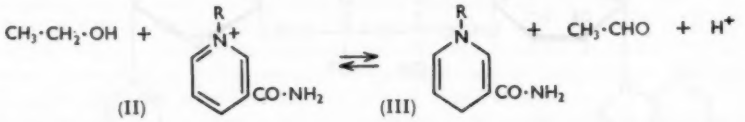
coenzyme field.[3,9] The carbodi-imide method[10] (see formulæ) seemed most suitable for initial study on account of its simplicity and because of the dipolar-ionic character and reducibility of nicotinamide nucleotides. In fact, it was successful to an unexpected degree, and consequently none of the other methods, which may also be equally applicable, has been tried.

Nicotinamide nucleotide is insoluble in anhydrous pyridine or dimethylformamide, the solvents used in our previous applications of the carbodi-imide method to the synthesis of nucleotide pyrophosphates.[7,11] However, Khorana has shown that aqueous pyridine can be used satisfactorily, for example in the self-condensation of adenosine-5′ phosphate, provided that a vast excess of the carbodi-imide is added.[12] This technique was applied to a mixture of nicotinamide nucleotide and adenosine-5′ phosphate; the latter compound, being much the more accessible, was used in excess. Examination of the reaction mixture by paper chromatography and electrophoresis showed the presence of all the expected products, *viz.*, diphosphopyridine nucleotide and the two symmetrical pyrophosphates, together with some of the starting materials. On anion-exchange chromatography, neither the nicotinamide nucleotide nor the symmetrical pyrophosphate derived from it—both effectively neutral—was retained by the resin, while the diphosphopyridine nucleotide, adenosine-5′ phosphate, and P^1P^2-diadenosine-5′ pyrophosphate were successively eluted with increasing strengths of formic acid.[13] A partial separation of nicotinamide nucleotide from the corresponding symmetrical pyrophosphate was achieved by cation-exchange chromatography and thus the proportions of all the components of the reaction mixture could be estimated. Almost half the nicotinamide nucleotide had been converted into diphosphopyridine nucleotide and only about a tenth into the symmetrical P^1P^2-di-(nicotinamide nucleoside) pyrophosphate. Since the latter compound is stable under the conditions of reaction there is evidently some hindrance to its formation. A similar phenomenon has been observed in the condensation of choline phosphate and cytidine-5′ phosphate effected by di*cyclo*hexylcarbodi-imide in aqueous pyridine:[14] none of the



expected P^1P^2-dicholine pyrophosphate could be detected. There would be little purpose in speculating here about the way in which the interaction of charges in a dipolar ion may affect participation in a condensation caused by a carbodi-imide; it suffices to note that such cases appear to be particularly favourable for application of the carbodi-imide method. Apparently the trifluoroacetic anhydride method does not share this useful selectivity.[6]

The synthetic diphosphopyridine nucleotide was isolated after ion-exchange chromatography as an amorphous powder, which had the correct elementary composition and a coenzyme content of about 70% according to spectroscopic assay with alcohol dehydrogenase.[15] This value was of the expected order because the synthesis had started from nicotinamide nucleotide containing the β- and the α-anomer in approximately 80 : 20 ratio and the optical rotation stood in the same relation to the published values[16] for the β- and the α-form of the coenzyme obtained from natural sources. Careful elution of the synthetic material from an anion-exchange column also suggested the presence of

[9] Todd, *Proc. Roy. Soc.*, 1954, *A*, **226**, 70.
[10] Khorana and Todd, *J.*, 1953, 2257.
[11] Kenner, Todd, and Webb, *J.*, 1954, 2843.
[12] Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3517.
[13] Cf. Kornberg and Pricer, *Biochemical Preparations*, 1953, **3**, 20.
[14] Kennedy, *J. Biol. Chem.*, 1956, **222**, 185.
[15] Racker, *ibid.*, 1950, **184**, 313.
[16] Kaplan, Ciotti, Stolzenbach, and Bachur, *J. Amer. Chem. Soc.*, 1955, **77**, 815.

two components, and comparison with natural material showed that the β-isomer was more easily eluted, as would be expected from the greater proximity of the positive and negative charges. But there seemed little hope of a practical separation by this means and there was no sign at all of separation by paper chromatography or electrophoresis even in presence of borate ions. However, a simple and efficient way of purifying the β-isomer was offered by its selective reduction with alcohol dehydrogenase. It is well known [5] that quaternary nicotinamide nucleotides (II) are easily decomposed by alkali, whereas their dihydro-derivatives (III) are stable to alkali although easily hydrolysed by acid. Consequently the α-isomer should, in principle, be completely removed by successive enzymic reduction, alkaline treatment, enzymic oxidation, and ion-exchange chromatography. In practice, the material recovered after this series of operations, which again had the correct elementary analysis, was identical with the natural coenzyme in paper chromatographic, electrophoretic, and ion-exchange behaviour, and appeared to be 90% pure as judged by both optical rotation and enzymic assay with alcohol dehydrogenase. Our tests were made by two observers over a period of several months and gave values diminishing steadily with time from 93 to 85%; commercial "95—100% cozymase" gave in our hands a value of 75% by the same method. Independent tests of our synthetic material with alcohol, lactate, and α-glycerophosphate dehydrogenases, which were very kindly carried out by Dr. M. Dixon in Cambridge and Dr. D. E. Hughes in Oxford, gave values about 65%. The discrepancy in these results is not as remarkable as it may appear at first sight. All the assays depend on measuring the absorption of light at 340 mμ, generated by enzymic action and associated with dihydro-coenzyme (III). A published survey [17] shows the wide variation in the extinction coefficients ascribed by various workers to the dihydro-coenzyme. Expressed in another way, these variations would correspond to different estimates of purity, if the same extinction coefficient was used. Throughout the present series of tests the value, 6220, which has been established by the ingenious work of Horecker and Kornberg,[18] was adopted. Perhaps the best identification of diphosphopyridine nucleotide is the absorption spectrum of its dihydro-derivative, which is compounded from those of the adenine and dihydronicotinamide chromophores. (The spectrum of the coenzyme itself is not particularly characteristic because the absorptions of the two chromophores are superimposed.) Unfortunately, and very surprisingly, so far as we have been able to discover, an absorption spectrum with the extinction coefficient 6220 at 340 mμ has never been recorded. Ohlmeyer [19] reported the isolation of dihydrocozymase with extinction coefficient 6270, but the actual spectrum was not recorded. Our Figure shows the close correspondence between the absorption curve of our material and those reproduced in standard works.[20, 21] We conclude that our synthetic diphosphopyridine nucleotide is at least comparable in purity with the best samples from natural sources.

The synthesis of diphosphopyridine nucleotide here described could be held to constitute also a synthesis of triphosphopyridine nucleotide (TPN, coenzyme II, codehydrogenase II), because treatment with phosphoryl chloride produces material with the appropriate coenzyme activity.[22] However, the purification of this material has not been described and therefore it seemed worth while to examine a more rational scheme of synthesis. The structure of triphosphopyridine nucleotide has been established as (I; R = PO_3H_2) by Kornberg and Pricer, who degraded the coenzyme enzymically to nicotinamide nucleotide and adenosine-2′ : 5′ diphosphate.[23] As the mixed adenosine-2′ : 5′ and -3′ : 5′

[17] Drabkin, *J. Biol. Chem.*, 1945, **157**, 563.
[18] Horecker and Kornberg, *ibid.*, 1948, **175**, 385.
[19] Ohlmeyer, *Biochem. Z.*, 1938, **297**, 66.
[20] Schlenk, "The Enzymes" (ed. Sumner and Myrbäck), Academic Press, New York, 1951, Vol. II, p. 267.
[21] Hasse, "Moderne Methoden der Pflanzenanalyse" (ed. Paech and Tracey), Springer, Berlin, 1955, Vol. IV, p. 322.
[22] Schlenk, *Naturwiss.*, 1937, **25**, 668.
[23] Kornberg and Pricer, *J. Biol. Chem.*, 1950, **186**, 557.

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diphosphate can be made readily from adenosine,[2] it was an obvious step to try the reversal of this hydrolysis with di*cyclo*hexylcarbodi-imide in aqueous pyridine. The product appeared on paper chromatography and electrophoresis to be the expected mixture, and the triphosphopyridine nucleotide fraction was separated in about 25% yield by anion-exchange chromatography.[24] Although the amorphous powder had the correct elementary analysis and ultraviolet absorption, small amounts of nicotinamide nucleotide and adenosine diphosphate were detected in it by paper electrophoresis. We believe that these arose, through decomposition after the ion-exchange separation, from those isomers of the coenzyme carrying the phosphate at position 3′. Such decomposition is easy to imagine, and it is worthy of note that coenzyme A, which has an analogous structure in the sense that it too bears a 3′-phosphate residue in the adenosine portion of the molecule, is relatively unstable. The coenzyme activity in the glucose 6-phosphate dehydrogenase system was kindly examined by Dr. M. Dixon, who found about 14% of the theoretical value. This value is in the expected region, since the material is presumably a mixture of four isomers. Enzymic purification of the β, 2′-isomer should be feasible, although there is not such a convenient enzyme for this purpose as in the case of the cozymase isomers.

Although this experiment undoubtedly yielded synthetic triphosphopyridine nucleotide, it is clearly only of a preliminary nature and further work is required.

Experimental

Condensation of Nicotinamide Nucleotide and Adenosine-5′ Phosphate.—Pyridine (325 c.c.) and then di*cyclo*hexylcarbodi-imide (18 c.c.) were added to a solution of nicotinamide nucleotide (1·0 g., 3 mmoles) and adenosine-5′ phosphate (2·0 g., 5·8 mmoles) in water (75 c.c.). The solution was kept overnight at 0° and then filtered from *s*-di*cyclo*hexylurea, which was extracted with hot water (10 c.c.). A second equal portion of the carbodi-imide was added to the combined filtrate and extract, which was kept at 0° for a further 24 hr. This process was repeated thrice so that in all 90 c.c. of carbodi-imide were used. Finally the solution was poured into water (2 l.). After 2 hr. the solution was filtered, washed with chloroform (3 × 350 c.c.), and concentrated (to 50 c.c.) under reduced pressure. The solution (pH 6·0) was put on a column (14 cm. × 8 cm.^{2}) of Dowex-2 resin (formate form), which was washed with water (400 c.c.). The aqueous washings (A) contained all the nicotinamide nucleotide and P^1P^2-di(nicotinamide nucleoside) pyrophosphate while the diphosphopyridine nucleotide and other products remained adsorbed on the resin (B).

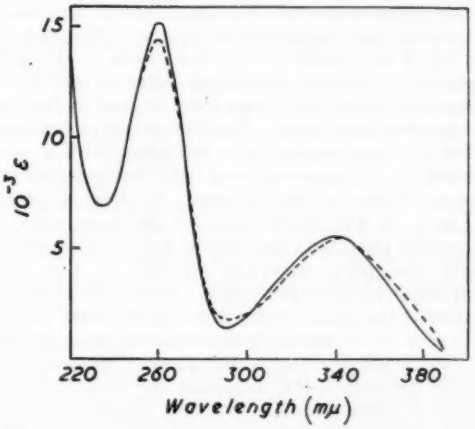
(A) The gum, obtained by evaporating the aqueous eluate, was dissolved in 0·1N-formic acid (10 c.c.) and added to a column (17 cm. × 2 cm.^{2}) of Dowex-50 resin (hydrogen form). When the column was developed with 0·1N-formic acid and 10 c.c. fractions were collected, the peak of the pyrophosphate band was found in tube 16 and the peak of mononucleotide band in tube 22. The separation was incomplete both in this experiment and in subsequent ones with longer columns.

(B) The Dowex-2 column was washed with 0·001N-formic acid (1 l.) before the diphosphopyridine nucleotide was eluted with 0·01N-formic acid (1·5 l.), the adenosine-5′ phosphate with 0·1N-formic acid (1·5 l.), and the P^1P^2-diadenosine-5′ pyrophosphate with N-formic acid (1·5 l.). The amounts of material eluted from the two columns were estimated from the light absorption at 260 mμ (the molar extinction coefficients given in parentheses) as follows: diphosphopyridine nucleotide (18,000) 1·40 mmoles; adenosine-5′ phosphate (14,000) 1·64 mmoles; P^1P^2-di-adenosine-5′ pyrophosphate (28,000) 0·95 mmole; nicotinamide nucleotide (5000) 0·63 mmole; P^1P^2-di(nicotinamide nucleoside) pyrophosphate (10,000) 0·17 mmole. The gum left after evaporation of the 0·01N-formic acid eluate was dissolved in water (20 c.c.) and freed from traces of cupric ion (from the distilled water) by passage through a column (2 cm. × 6 cm.^{2}) of Dowex-50 resin (hydrogen form), which was washed with water (400 c.c.). The combined solution and washings were concentrated to 30 c.c. before being added dropwise to " AnalaR " acetone (400 c.c.). The flocculent colourless precipitate was kept for several hours before removal by centrifugation and washing with acetone (200 c.c.). At this stage the diphosphopyridine nucleotide (0·935 g., 1·4 mmoles) had $[\alpha]_D^{20}$ −24·5° (±0·5°) (*c* 5·5 in H_2O) (Found, in

[24] Cf. Kornberg and Horecker, *Biochemical Preparations*, 1953, **3**, 24.

material dried at 20°/10^{-3} mm.: C, 36·9; H, 4·5; N, 14·2; P, 9·0. Calc. for $C_{21}H_{27}O_{14}N_7P_2,H_2O$: C, 37·0; H, 4·3; N, 14·4; P, 9·1%).

Enzymic Purification of Diphosphopyridine Nucleotide.—A suspension (0·1 c.c. containing 3 mg. of crystalline enzyme; Boehringer G.m.B.H., Mannheim) of alcohol dehydrogenase and ethanol (30 c.c.) were added to a solution of the foregoing material (0·200 g.) in 0·01M-glycine buffer (500 c.c.; pH 9·0). After 3 hr. the optical density at 340 mμ had become constant and 10% sodium hydroxide solution (20 c.c.) was added. The mixture was kept during 12 hr. at 20° and its pH was then adjusted to 9·0 with 3N-hydrochloric acid. The solution was concentrated to 250 c.c. and then diluted with water to 500 c.c. A second portion (0·1 c.c.) of alcohol dehydrogenase solution, and acetaldehyde (0·5 c.c.), were added; in 10 min. the light absorption at 340 mμ had vanished. The solution was brought to pH 3 with 3N-hydrochloric acid before being concentrated to 150 c.c. It was then added to a column (10 cm. × 20 cm.²) of Dowex-50 resin (lithium form), which was washed with water (300 c.c.). The aqueous eluate was concentrated to 2 c.c. and then diluted with a mixture of acetone (150 c.c.) and ethanol (50 c.c.). The precipitate was collected by centrifugation, washed with a second portion of ethanolic acetone, and dissolved in water (100 c.c.). The solution was concentrated to 50 c.c. and then added to a column (3 cm. × 12 cm.²) of Dowex-2 resin (formate form). The column was washed with 0·001N-formic acid (1 l.) before the coenzyme was eluted with 0·01N-formic



Absorption spectrum of synthetic diphosphopyridine nucleotide (—) after reduction with alcohol dehydrogenase; and absorption spectrum of the natural dihydrocoenzyme (– – – – –).[20]

acid (1·5 l.). The coenzyme was recovered as a gum by evaporation of the formic acid, and it was then precipitated by " AnalaR " acetone (200 c.c.) from water (2 c.c.) and washed with acetone (100 c.c.). The product (0·091 g.) had $[\alpha]_D^{20}$ −31·5° (±0·5°) (*c* 1·2 in H_2O) {Kaplan *et al.*[16] give $[\alpha]_D^{23}$ −34·8° (*c* 1 in H_2O)}, light absorption $\varepsilon_{max.}$ 18,100 (*M* 681) at 260 mμ (Found, in material dried at 20°/10^{-3} mm.: C, 37·5; H, 4·9; N, 14·1; P, 9·0. $C_{21}H_{27}O_{14}N_7P_2,H_2O$ requires C, 37·0; H, 4·3; N, 14·4; P, 9·1%). The behaviour of samples (about 1 mg.) of the synthetic and the natural material on a column (8 cm. × 1 cm.²) of Dowex-2 resin (acetate form) was compared. Elution of the two materials by 0·1N-acetic acid followed a very similar pattern, with the peak at about 170 c.c. On the other hand a very broad peak centred about 310 c.c. was produced by some synthetic diphosphopyridine nucleotide which contained only 30% of coenzyme; it had been prepared from nicotinamide nucleotide which was mainly the α-anomer and it had not been enzymically purified.

Determination of Coenzyme Activity with Alcohol Dehydrogenase.—The following experiment is typical; concordant results were obtained by slightly different techniques, for example with 0·1M-disodium hydrogen phosphate instead of the glycine buffer. Ethanol (1 c.c.) and synthetic diphosphopyridine nucleotide (1·212 mg.) were made up to 25·0 c.c. with 0·01M-glycine–sodium glycine buffer (pH 9·0). The optical density of this solution was measured in a 1 cm. cell at 260 mμ (1·29) and 340 mμ (0·007) against a cell filled with ethanolic buffer. A small quantity of alcohol dehydrogenase was then added to each cell. In 15 min. the optical density at 340 mμ had become constant (0·400), and the complete spectrum was determined (see Figure). The

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increase (0·393) in optical density at 340 mμ was 88·5% of that expected for the dihydrocoenzyme (ε 6220 [18]) produced from hydrated diphosphopyridine nucleotide (*M* 681). In other experiments it was shown that the light absorption at 340 mμ was destroyed by addition of excess of acetaldehyde.

Condensation of Nicotinamide Nucleotide with a Mixture of Adenosine-2′ : 5′ and -3′ : 5′ Diphosphate.—Pyridine (75 c.c.) and then di*cyclo*hexylcarbodi-imide (6 c.c.) were added to a solution of nicotinamide nucleotide (0·30 g.) and the mixed adenosine diphosphates [2] (0·80 g.) in water (15 c.c.). The mixture was kept at 20° and three more equal portions of carbodi-imide were added at intervals of 2 days. After 8 days in all, water (700 c.c.) was added and the *s*-di*cyclo*hexylurea was removed. The filtrate was washed with ether (2 × 300 c.c.), concentrated to 30 c.c., and treated with N-hydrochloric acid (8 c.c.). After 4 hr. the precipitated di*cyclo*hexylurea was removed and the solution was neutralised (pH 7·0) with lithium hydroxide. The solution was evaporated to a syrup which was shaken with alcohol (25 c.c.) and acetone (75 c.c.). The resulting brown precipitate was washed with a second portion of ethanolic acetone before being dissolved in water (25 c.c.) and added to a column (8 cm. × 5 cm.^{2}) of Dowex-2 resin (chloride form). Most of the nicotinamide nucleotide and P^1P^2-di(nicotinamide nucleoside) pyrophosphate were removed by washing the column with water (500 c.c.), but small amounts were contained in the first fractions during the main elution. This was carried out with 0·1N-formic acid–0·1M-sodium formate, 50 c.c. fractions being collected. The triphosphopyridine nucleotide was contained in fractions 10—50 (peak at fraction 22), which were combined and evaporated to dryness. The residue was dissolved in water (300 c.c.), one-third of which was added to a column (7 cm. × 20 cm.^{2}) of Dowex-50 resin (hydrogen form). The column was washed with water (500 c.c.) until no more light-absorbing material was removed. The other two-thirds were then treated in the same way and the combined washings were evaporated to dryness. The residue was precipitated from water (5 c.c.) by " AnalaR " acetone (200 c.c.) and washed at a centrifuge with a second portion of acetone before being dried (0·154 g.). It had maximum light absorption at 260 mμ (ε 18,150 calc. with *M* 797) (Found, in material dried at 20°/10^{-3} mm.: C, 31·7; H, 4·8; N, 11·7. Calc. for $C_{21}H_{28}O_{17}N_7P_3,3H_2O$: C, 31·7; H, 4·3; N, 12·3%). Dr. M. Dixon reported that, when this material was treated with glucose 6-phosphate and glucose 6-phosphate dehydrogenase in phosphate buffer (pH 7·4), the light absorption developed at 340 mμ was 14% of that expected for pure anhydrous triphosphopyridine nucleotide. Paper electrophoresis showed that it contained, in addition to material travelling at the same speed as the natural coenzyme, small amounts of adenosine-2′ : 5′ or -3′ : 5′ diphosphate and nicotinamide nucleotide.

Paper Electrophoresis and Paper Chromatography of the Nucleotides.—Electrophoresis was much the more useful technique (see Table); it was carried out for 6 hr. on Whatman no. 54 paper in 0·05M-disodium hydrogen phosphate (pH 8·0) at a potential gradient of about 5 v/cm. (220 v applied). Whatman no. 1 paper was used for ascending chromatography with butan-1-ol–acetic acid–water (5 : 2 : 3) (system A) or *iso*butyric acid–N-ammonia containing ethylenediaminetetra-acetic acid (5 : 3) (system B).[25]

Substance	Migration (cm.)	R_P in system A	R_P in system B
Nicotinamide nucleotide	3·4	0·18	0·41
P^1P^2-Di(nicotinamide nucleoside)pyrophosphate	−1·0	0·08	—
Adenosine-5′ phosphate	6·2	0·17	0·52
Adenosine-2′ : 5′ or -3′ : 5′-diphosphate	10·5	0·09	0·30
P^1P^2-Diadenosine-5′ pyrophosphate	4·6	0·06	—
Diphosphopyridine nucleotide	1·9	0·10	0·46
Triphosphopyridine nucleotide	6·7	0·06	0·27

We thank the Rockefeller Foundation for its support and the Department of Scientific and Industrial Research for a Maintenance Grant (to N. A. H.). We are also deeply indebted to Dr. M. Dixon, Biochemistry Department, Cambridge, and Dr. D. E. Hughes, Biochemistry Department, Oxford, for generously making independent enzymic tests.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 28th*, 1957.]

[25] Krebs and Hems, *Biochim. Biophys. Acta*, 1953, **12**, 172.

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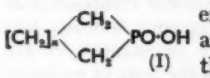
736. *The Dissociation Constants of Some Cyclic Phosphinic Acids.*

By Gennady M. Kosolapoff and Robert F. Struck.

Synthesis of tetramethylene- and trimethylene-phosphinic acid was accomplished by organometallic routes. These acids and the previously reported pentamethylenephosphinic acid were shown to possess acidic dissociation constants indicative of stronger acidic properties than shown by analogous dialkylphosphinic acids.

In continuation of a study of acidic properties of acids of phosphorus,[1] we prepared and examined tetramethylene- and trimethylene-phosphinic acid (I; $n = 2$ and 1, respectively), as progressively more strained cyclic analogues of the previously reported pentamethylenephosphinic acid.[2]


(I)

The yield of tetramethylenephosphinic acid, prepared as described for the pentamethylene analogue,[2] was only 0·1% and, although models show no steric strain to account for this, they do account for the still smaller yield of the trimethylene analogue, which was prepared by ring closure of 3-bromopropylphosphonic dichloride, with magnesium, because of the impossibility of preparing the bifunctional Grignard reagent from 1 : 3-dibromopropane.

The apparent pK values for acidic dissociation of these acids, as well as for the analogous dialkylphosphinic acids, are shown in the Table.

Acid	pK_a'	Acid	pK_a'
$[CH_2]_3{>}PO_2H$	3·07	Me_2PO_2H [1]	3·08
$[CH_2]_4{>}PO_2H$	2·51	Et_2PO_2H [1]	3·29
$[CH_2]_5{>}PO_2H$	2·73	$Pr^n{}_2PO_2H$ [1]	3·46

It is evident that the cyclic acids are somewhat stronger acids than are their dialkyl, or open chain, analogues. There is not evident any definite trend of acidity amongst the three cyclic members reported here, *i.e.*, no relation of acidity to position in the homologous series. This is contrary to what was discovered by us amongst the dialkylphosphinic acids,[1] which showed excellent correlation of acidity with structure.

Experimental

Tetramethylenephosphinic Acid.—The acid was prepared by the method used previously for the synthesis of pentamethylenephosphinic acid,[2] but with the bifunctional Grignard reagent from tetramethylene bromide. The crude acid was converted by means of phosphorus pentachloride into its chloride which boiled at 1·3 mm. over the range of 64—107° and was effectively separated from polymeric materials. The crude chloride was hydrolysed to the free acid by means of warm water and the acid was isolated by evaporation, dissolution in a small volume of benzene, and precipitation with *n*-heptane. The acid was finally purified by extraction with hot *n*-heptane and cooling; the acid formed colourless flakes which, after being dried *in vacuo*, melted at 99—100° (Found: P, 25·6. $C_4H_9O_2P$ requires P, 25·8%). The yield of the pure *acid* was 100 mg. from 93 g. of tetramethylene bromide.

Trimethylenephosphinic Acid.—Trimethylene bromide (202 g.) and triethyl phosphite (33·2 g., 5 mols.) were refluxed until the evolution of ethyl bromide had ceased. The resulting diethyl 3-bromopropylphosphonate was hydrolysed *in situ* with 48% hydrobromic acid as described previously.[3] The acid, m. p. 106—107°, was obtained in average yield of 88%. This acid (30 g.) was treated with phosphorus pentachloride (65 g.), suspended in carbon tetrachloride (250 ml.), and yielded, after 2 hours' refluxing, 3-bromopropylphosphonic dichloride (14·7 g., 40%), b. p. 153—156°/23 mm. The relatively low yield of the dichloride was caused by the formation of undistillable tar during the distillation. The dichloride decomposes rather vigorously, with evolution of hydrogen bromide, when heated to ~180°. The dichloride was also prepared through the corresponding di*iso*propyl ester, b. p. 100°/1 mm., obtained in 56·5% yield from trimethylene bromide (300 g.) and tri*iso*propyl phosphite (100 g.); the yield of

[1] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3379.
[2] Kosolapoff, *ibid.*, 1955, **77**, 6658.
[3] Kosolapoff, *ibid.*, 1944, **66**, 1511.

the ester was relatively poor because of incipient decomposition and evolution of hydrogen bromide which began after a major part of the ester had distilled.

3-Bromopropylphosphonic dichloride (93·1 g.), in dry ether (50 ml.), was added during 34 hr. to a stirred mixture of ether (600 ml.), magnesium turnings (9·4 g.) and iodine (1 crystal), under gentle reflux. Refluxing for 12 hr. gave no evidence of further reaction, the mixture at this juncture containing an orange-red precipitate (some 30 g.) and some 2 g. of magnesium. These components were separated mechanically. The ethereal solution was worked up as described for the tetramethylene and the pentamethylene analogues,[2] yielding a very small amount of a wax which was combined with the major part of the product described below. The orange-red solid was treated with ice and hydrochloric acid: a strong " phosphine " odour then became evident, indicating the presence of either tervalent phosphorus compounds or those with a phosphorus–phosphorus link. Accordingly, the crude aqueous solution was treated with 30% hydrogen peroxide (20 ml.) to oxidize any such substances to the quinquevalent state. The resulting solution was concentrated to remove the bulk of excess of hydrochloric acid, and the residual solution was freed from magnesium ions by means of an ion-exchange resin, and from the bulk of polymeric products and phosphonic acids by treatment with barium hydroxide, as described previously.[2] The resulting crude product was distillable in a high vacuum at approximately 100—120°, but the distilled product failed to crystallise. It was taken up in water, along with the small amount of product derived from the ethereal solution, described above, and neutralised with lead oxide at 50—60°. The clear filtrate from the precipitated insoluble lead salts (and excess of lead oxide) was treated with hydrogen sulphide. The residual solution, after removal of lead sulphide, was evaporated to dryness, yielding a colourless solid, which was extracted for 5 days with boiling benzene. The extract on evaporation gave 12 mg. of *trimethylenephosphinic acid* which melted unsharply at 65°, passing into a glass from which it crystallised to small flat needles only with extreme slowness (Found: P, 29·0. $C_3H_7O_2P$ requires P, 29·2%).

One of the runs in which 3-bromopropylphosphonic acid was prepared gave a curious by-product. During the hydrolysis of the crude ester with hydrobromic acid a dense liquid was formed. This was separated and distilled, without decomposition. The substance, a colourless liquid, had b. p. 176—178°/15 mm., 124—125°/1·2 mm., d_4^{26} 2·0312, n_D^{26} 1·6237, and molecular weight (determined ebullioscopically in benzene) 583. The substance was free from phosphorus and contained 70·4% of bromine. These data are not inconsistent with a pentabromododecane which might result from tetramerization of trimethylene bromide, possibly through formation of allyl bromide, with subsequent addition of hydrogen bromide. This material was not observed in several other runs made apparently under identical conditions.

Dissociation Constants.—These were calculated from titration data as described earlier.[1]

We acknowledge our gratitude to The Dow Chemical Company for a gift of a quantity of trimethylene bromide.

Ross Chemical Laboratory, Alabama Polytechnic Institute,
Auburn, Alabama, U.S.A. [*Received, March 28th,* 1957.]

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737. iso*Shekkangenin and the Synthesis of* 4-*Hydroxycoumarins.*

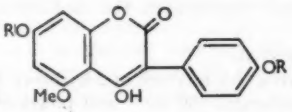
By A. H. Gilbert, A. McGookin, and Alexander Robertson.

Contrary to the suggestion by Chi *et al.*[1] *iso*shekkangenin is not identical with either 4 : 5 : 4′-trihydroxy-7-methoxy- or 4 : 7 : 4′-trihydroxy-5-methoxy-3-phenylcoumarin. The substitution of methyl chloroformate and potassium carbonate for ethyl carbonate and sodium in an earlier procedure [2] provides a general method for the synthesis of 4-hydroxycoumarins, including polyhydroxy-derivatives.

From the Chinese drug " shekkan " derived from *Balamacanda chinensis* (Linn) D.C. (identical with *Pardanthus chinensii* Ker Gawl [1]) Marmicke, Schumann, and Liss [3] isolated a glycoside shekkanin, which was shown by Shibata [4] to be identical with tectoridin, giving

[1] Chi, Hsu, Hu, and Wang, *J. Chinese Chem. Soc.*, 1947, **15**, 26.
[2] Boyd and Robertson, *J.*, 1948, 174.
[3] Marmick, Schumann, and Liss, *Arch. Pharm.*, 1937, **275**, 317.
[4] Shibata, *J. Pharm. Soc. Japan*, 1927, No. **543**, 380.

the aglucone tectorigenin. According to Chi, Hsu, Hu, and Wang [1] the variety of this drug obtained from another species of *Iridaceae, Iris wattii* Baker, contains an isomeric glycoside *iso*shekkanin $C_{22}H_{22}O_{11}$ which on hydrolysis gives a hexose and *iso*shekkangenin, $C_{15}H_9O_5{\cdot}OMe$, m. p. 228°, forming a triacetate, m. p. 184—185°, and a dimethyl ether, m. p. 157°. On hydrolytic fission with 10% alcoholic potassium hydroxide *iso*shekkangenin gave phloroglucinol monomethyl ether and *p*-hydroxyphenylacetic acid. From this the Chinese authors [1] suggested that the aglycone had structure (I; R = H) or a tautomer of it, but did not propose the alternative (II) equally possible on their experimental findings.



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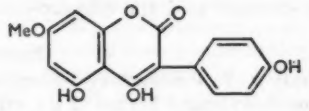

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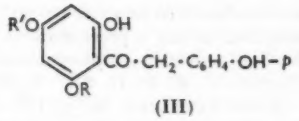
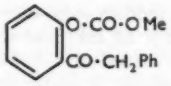
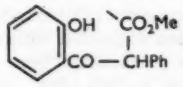


(III)



(IV)



(V)

The synthesis of the dimethyl ether (I; R = Me), m. p. 243—245°, has been effected by interaction of 2-hydroxy-4 : 6-dimethoxyphenyl 4-methoxybenzyl ketone and ethyl carbonate in the presence of sodium according to an earlier general method [2] but the synthetical compound did not appear to be identical with the dimethyl ether of *iso*shekkangenin. Since alternative orientations are possible for a dimethyl ether of (I; R = H) or (II), synthesis of the compounds (I; R = H) and (II) appeared to be essential.

Application of the ethyl carbonate–sodium method to 2 : 4-dihydroxy-6-methoxyphenyl 4-hydroxybenzyl ketone failed to give a 4-hydroxycoumarin and an investigation of this procedure with polyhydroxy-ketones was undertaken to ascertain its limitations. It was found that with ketones of the type (III), containing two free hydroxyl groups, extremely poor yields of the 4-hydroxycoumarins were obtained and with ketones having three or more free hydroxyl groups the reaction failed completely. In efforts to employ benzyl ethers difficulties arose in attempts to prepare polybenzyloxy-compounds, expecially of phloroglucinol derivatives, but the successful conversion of an impure tri(methoxycarbonyl) derivative of (III; R = Me, R' = H) with sodium into the coumarin (II) in small yield, and the use of carbonyl chloride in the synthesis of 3-acetyl-4-hydroxy-7-methoxycoumarin [5] suggested the use of methyl chloroformate in place of ethyl carbonate. Ultimately it was found that when an *o*-hydroxyacetophenone of the type (III) was heated with methyl (or ethyl) chloroformate and potassium carbonate in boiling acetone good yields of 4-hydroxycoumarins were obtained; further, the reaction was applicable to polyhydroxy-ketones, probably proceeding by way of the intermediates (IV) and (V), involving a Baker–Venkataraman rearrangement; the reaction did not proceed with sodium or pyridine in benzene in place of potassium carbonate–acetone. Comparably with the synthesis of *iso*flavones with ethoxalyl chloride (Baker *et al.*[6]), it was found that the chloroformate reaction required at least $(n + 1)$ mol. of ester where n is the number of hydroxyl groups present in the ketone. The crude product from polyhydroxy-ketones invariably appeared to contain one or more methoxycarbonyl groups which were hydrolysed with dilute alkali. The synthesis of a variety of 4-hydroxycoumarins by this method indicates the scope of the reaction but curiously, though phloropropiophenone gave a satisfactory yield of 4 : 5 : 7-trihydroxy-3-methylcoumarin, phloroacetophenone failed to yield a coumarin.

[5] Badcock, Dean, Robertson, and Whalley, *J.*, 1950, 903.
[6] Baker, Chadderton, Harbourne, and Ollis, *J.*, 1953, 1852.

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The 4-hydroxycoumarins (I; R = H) and (II) were prepared from the ketones (III; R = Me, R′ = H and *vice versa*, respectively) but these compounds and their triacetates differ markedly from *iso*shekkangenin and its triacetate. The ketone (III; R = H, R′ = Me) required for the synthesis of the coumarin (II) could not be prepared directly but was obtained by the regulated hydrolytic fission of synthetic 5 : 4′-dihydroxy-7-methoxy*iso*flavone (prunetin).

In examining possible alternative routes to 4-hydroxycoumarins 5 : 7 : 4′-trimethoxy-*iso*flavone was hydrogenated with a palladium–charcoal catalyst, giving 2 : 3-dihydro-5 : 7 : 4′-trimethoxy*iso*flavone but the 2-methylene group could not be oxidised to carbonyl: *e.g.*, with chromic acid the dihydro-compound regenerated the *iso*flavone.

Experimental

4-Hydroxy-5 : 7 : 4′-trimethoxy-3-phenylcoumarin.—A mixture of 2-hydroxy-4 : 6-dimethoxyphenyl 4-methoxybenzyl ketone (2 g.), ethyl carbonate (50 ml.), and powdered sodium (2 g.) was heated on the steam-bath until the reaction subsided. After the addition of a little methanol to decompose unchanged sodium the reddish sodio-derivative was dissolved in water (50 ml.), and the solution extracted with ether (2 × 25 ml.) and then acidified, giving a precipitate (1·2 g.) which on purification from alcohol furnished *4-hydroxy-5 : 7 : 4′-trimethoxy-3-phenylcoumarin*, needles, m. p. 243—245°, readily soluble in acetic acid (Found: C, 65·8; H, 5·1. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9%). The *acetate* separated from alcohol in needles, m. p. 177—178° (Found: C, 65·3; H, 4·9. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

The same ketone (2 g.) was heated with methyl chloroformate (1 ml.) and potassium carbonate (5 g.) in boiling acetone (50 ml.) for 4·5 hr. and the mixture poured into water (500 ml.). Acidification of this gave the coumarin (1·6 g.) which was washed with water and crystallised from dilute acetic acid, forming needles, m. p. and mixed m. p. 242—245°.

4 : 7 : 4′-Trihydroxy-5-methoxy-3-phenylcoumarin.—(*a*) Methyl chloroformate (2·7 ml., 3 mol.) was added dropwise to a cooled and agitated solution of 2 : 4-dihydroxy-6-methoxyphenyl 4-hydroxybenzyl ketone (2·5 g.) in 2·2% aqueous sodium hydroxide (100 ml.; 3 mol. of hydroxide). An hour later, the viscous yellow-brown product was isolated with ether, and the ethereal solution washed with dilute alkali and then water, dried, and evaporated. The residue, which did not crystallise and decomposed on attempted distillation in a high vacuum, was treated in dry benzene (50 ml.) with pulverised sodium (1 g.) and 1 drop of alcohol. This mixture was heated on the steam-bath to complete the reaction and mixed with a little methanol and then water (50 ml.). Acidification of the aqueous layer gave a buff precipitate which on purification from alcohol gave the *4 : 7 : 4′-trihydroxy-5-methoxy-3-phenylcoumarin* in small prisms (0·15 g.), m. p. 316—318°, fairly soluble in alcohol, ethyl acetate, or acetone and insoluble in benzene (Found: C, 63·3; H, 4·2; OMe, 10·3. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0; 1OMe, 10·33%). The *triacetate* formed slender needles, m. p. 200—202°, from alcohol (Found: C, 62·01; H, 4·44. $C_{22}H_{18}O_9$ requires C, 61·97; H, 4·26%).

(*b*) A mixture of ketone (2 g.), methyl chloroformate (2·3 ml.), potassium carbonate (7·5 g.), and acetone (50 ml.) was heated under reflux for 3 hr., poured into water (500 ml.), and acidified with concentrated hydrochloric acid. The solid (1·8 g.) was hydrolysed with warm N-aqueous sodium hydroxide (100 ml.) for 1 hr., cooled, diluted to 200 ml., filtered, and acidified. Crystallised from alcohol, the precipitate gave the coumarin in small prisms (1·4 g.), m. p. and mixed m. p. 317—318°.

4 : 5 : 4′-Trihydroxy-7-methoxy-3-phenylcoumarin.—A mixture of 5 : 4′-dihydroxy-7-methoxy-*iso*flavone (1 g.), trisodium phosphate (10 g.), and water (50 ml.) was heated under reflux for 1 hr., cooled, filtered, acidified, and extracted with ether (2 × 25 ml.). The extract was washed with sodium hydrogen carbonate solution, followed by water, dried, and evaporated, leaving *2 : 6-dihydroxy-4-methoxyphenyl 4-hydroxybenzyl ketone* which, on repeated purification from aqueous methanol, formed colourless needles, m. p. 247—249°, with a red-brown ferric reaction in alcohol (Found: C, 65·4; H, 5·2. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%). Mixed with *iso*flavone, the compound had m. p. 220—225°. This ketone (0·8 g.) was heated with methyl chloroformate (0·9 ml.) and potassium carbonate (2·5 g.) in boiling acetone (30 ml.) for 3 hr. and the mixture poured into water (250 ml.). The precipitate (0·65 g.) obtained by acidification of this was warmed with N-aqueous sodium hydroxide (50 ml.) for 1 hr., and the cooled mixture diluted with water (50 ml.), filtered, and acidified. Crystallised from dilute

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alcohol, the precipitate gave 4 : 5 : 4′-trihydroxy-7-methoxy-3-phenylcoumarin in needles (0·5 g.), m. p. 300—302°, soluble in acetic acid, alcohol, or acetone and having a greenish-blue ferric reaction in alcohol (Found: C, 64·0; H, 4·1. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%). The *triacetate* formed clusters of needles, m. p. 206—208°, from alcohol (Found: C, 62·2; H, 4·3. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·3%).

4-Hydroxy-5 : 7-dimethoxy-3-phenylcoumarin.—On acidification the mixture obtained from the reaction of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (2 g.), diethyl carbonate (50 ml.), and pulverised sodium (2 g.) on the steam-bath gave *4-hydroxy-5 : 7-dimethoxy-3-phenylcoumarin* which separated from alcohol in fine needles (1·2 g.), m. p. 204—205° (Found: C, 68·5; H, 4·7; OMe, 19·1. $C_{17}H_{14}O_5$ requires C, 68·45; H, 4·7; 2OMe, 20·8%). The same coumarin (1·4 g.), m. p. and mixed m. p. 203—205°, after purification was obtained from a mixture of the ketone (2 g.), methyl chloroformate (1·1 ml.), and potassium carbonate (2·5 g.) kept in boiling acetone (30 ml.) for 3 hr. The *acetate* separated from alcohol in slender needles, m. p. 168—170° (Found: C, 67·3; H, 4·9. $C_{19}H_{16}O_6$ requires C, 67·05; H, 4·75%).

Boiled with a mixture of hydriodic acid (20 ml.; *d* 1·7), acetic acid (10 ml.), and acetic anhydride (10 ml.), this coumarin (1 g.) gave 4 : 5 : 7-*trihydroxy-3-phenylcoumarin* which separated from aqueous alcohol and then ethyl acetate–benzene in prisms, m. p. 278—280°, soluble in aqueous sodium hydrogen carbonate and having a blue-green ferric reaction in alcohol (Found: C, 66·9; H, 4·0. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). The same coumarin (0·8 g.) was prepared by the methyl chloroformate–potassium carbonate method from benzyl 2 : 4 : 6-trihydroxyphenyl ketone (1 g.), having m. p. and mixed m. p. 278—280° and forming the same *triacetate* which separated from alcohol in needles, m. p. 209—210° (Found: C, 64·0; H, 4·3. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·3. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·1%).

4 : 7-Dihydroxy-5-methoxy-3-phenylcoumarin.—The interaction of phloroglucinol monomethyl ether (3 g.), benzyl cyanide (3 g.), and zinc chloride (1 g.) in ether (50 ml.) saturated with hydrogen chloride at 0° followed by hydrolysis of the product gave *benzyl 2 : 4-dihydroxy-6-methoxyphenyl ketone*, which formed plates (2·1 g.), m. p. 145—146°, from aqueous methanol, having a red-brown ferric reaction (Found: C, 69·8; H, 5·4; OMe, 12·1. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4; 1OMe, 12·1%). By the ethyl chloroformate–potassium carbonate method and treatment of the product with warm N-aqueous sodium hydroxide this ketone (2 g.) gave 4 : 7-*dihydroxy-5-methoxy-3-phenylcoumarin* which separated from alcohol in tiny needles (1·8 g.), m. p. 292—293° (Found: C, 67·8; H, 4·3. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%), forming a *diacetate*, slender needles, m. p. 224—225° (from alcohol) (Found: C, 64·9; H, 4·4. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%).

4 : 4′-Dihydroxy-5 : 7-dimethoxy-3-phenylcoumarin.—By the sodium–ethyl carbonate (yield, *ca.* 30%) or by the methyl chloroformate–potassium carbonate method (yield, *ca.* 80%), 4-hydroxybenzyl 6-hydroxy-2 : 4-dimethoxyphenyl ketone gave *4 : 4′-dihydroxy-5 : 7-dimethoxy-3-phenylcoumarin*, forming needles, m. p. 280—282°, from alcohol (Found: C, 64·9; H, 4·5; OMe, 18·3. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5; 2OMe, 19·7%); its *diacetate* formed needles, m. p. 212—214°, from alcohol (Found: C, 63·6; H, 4·7. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·55%).

The following 4-hydroxycoumarins were prepared by heating the requisite benzyl *o*-hydroxyphenyl ketone with excess of methyl chloroformate and potassium carbonate in boiling acetone for 3 hr. and subsequent treatment of the product with N-aqueous sodium hydroxide (warm or at room temperature). The end of the reaction was clearly indicated when the mixture became yellow and superheated; the yields varied from 75 to 85%. Coumarins with a free hydroxyl group in the 5-position gave a violet or deep blue-green ferric reaction in alcohol.

4 : 5 : 7 : 4′-Tetrahydroxy-3-phenylcoumarin, from 4-hydroxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone, in tiny prisms, m. p. 334—336°, from alcohol, identical with a specimen (0·4 g.) prepared by the demethylation of 4-hydroxy-5 : 7 : 4′-trimethoxy-3-phenylcoumarin (1 g.) with hydriodic acid (Found, in anhydrous specimen: C, 63·1; H, 3·5. $C_{15}H_{10}O_6$ requires C, 63·0; H, 3·5%), and giving a *tetra-acetate*, prisms, m. p. 196—198° (from alcohol) (Found: C, 60·5; H, 4·0. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%).

4 : 5 : 7-Trihydroxy-4′-methoxy-3-phenylcoumarin, from 4-methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (2 g.), in needles (1·4 g.), m. p. 308—310°, from dilute alcohol (Found: C, 64·1; H, 4·3. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%), giving a *triacetate* in needles, m. p. 208—210°, from the same solvent (Found: C, 62·1; H, 4·2. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·3%).

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4 : 7-*Dihydroxy*-5 : 4′-*dimethoxy*-3-*phenylcoumarin*, from 2 : 4-dihydroxy-6-methoxyphenyl 4-methoxybenzyl ketone, in long needles, m. p. 258—260°, from alcohol (Found: C, 65·3; H, 4·6. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%), gave a *diacetate* in rosettes of needles, m. p. 207—209°, from the same solvent (Found: C, 63·5; H, 4·7. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·55%). The *ketone* was prepared from phloroglucinol monomethyl ether and *p*-methoxybenzyl cyanide (Hoesch reaction), and formed slender needles, m. p. 166—167°, from dilute methanol (charcoal), with a wine-red ferric reaction (Found: C, 66·5; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%).

4-*Hydroxy*-5 : 7 : 2′-*trimethoxy*-3-*phenylcoumarin*, from 2-methoxybenzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone, in needles, m. p. 246—248°, from 50% acetic acid (Found: C, 65·7; H, 4·9; OMe, 28·1. $C_{18}H_{16}O_6$ requires C, 65·85; H, 4·9; OMe, 28·3%), gave an *acetate* in needles, m. p. 185—188°, from alcohol (Found: C, 65·3; H, 5·1. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

4 : 5 : 7-*Trihydroxy*-2′-*methoxy*-3-*phenylcoumarin*, from 2-methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone in needles, m. p. 306—308°, from dilute alcohol (Found: C, 64·1; H, 4·2. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%), gave a *triacetate* in needles, m. p. 200—201°, from alcohol (Found: C, 62·2; H, 4·3. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·3%).

4 : 7-*Dihydroxy*-5 : 2′-*dimethoxy*-3-*phenylcoumarin*, from 2 : 4-dihydroxy-6-methoxyphenyl 2-methoxybenzyl ketone, in minute needles, m. p. 264—266°, from ethyl acetate (Found: C, 65·0; H, 4·6. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%) [*diacetate*, prisms, m. p. 226—227°, from alcohol (Found: C, 63·6; H, 4·7. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·55%)].

4-*Hydroxy*-5 : 7 : 3′-*trimethoxy*-3-*phenylcoumarin*, from 2-hydroxy-4 : 6-dimethoxyphenyl 3-methoxybenzyl ketone, m. p. 179—180°, from dilute acetic acid (Found: C, 65·8; H, 5·0; OMe, 27·1. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9; OMe, 28·35%), furnished an *acetate* in silky needles, m. p. 168—170°, from alcohol (Found: C, 65·3; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%). Prepared by the Hoesch method from phloroglucinol (4 g.), 3-*methoxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone* separated from 90% methanol in cubes (2·6 g.), m. p. 168—169°, with an intense red-brown ferric reaction (Found: C, 66·5; H, 5·2. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%). With methyl sulphate (2·2 ml.) and potassium carbonate (10 g.) in boiling acetone (50 ml.) for 3 hr. this ketone (3 g.) gave **2-*hydroxy*-4 : 6-*dimethoxyphenyl* 3-*methoxybenzyl ketone***, forming needles (2·3 g.), m. p. 66—67°, from methanol, with a red-brown ferric reaction (Found: C, 67·7; H, 6·1. $C_{17}H_{18}O_5$ requires C, 67·6; H, 6·0%).

4 : 5 : 7-*Trihydroxy*-3′-*methoxy*-3-*phenylcoumarin*, from 3-methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone, in needles, m. p. 296—297°, from dilute alcohol (Found, in anhydrous specimen: C, 64·1; H, 4·2. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%), gave a *triacetate* in long needles, m. p. 210—212°, from alcohol (Found: C, 62·1; H, 4·3. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·3%).

Prepared from 2 : 4-dimethoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone by methyl sulphate–potassium carbonate, **2 : 4-*dimethoxybenzyl* 2-*hydroxy*-4 : 6-*dimethoxyphenyl ketone*** formed glistening plates, m. p. 136—137°, from methanol, with a red ferric reaction (Found: C, 64·6; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·1%), and gave 4-*hydroxy*-5 : 7 : 2′ : 4′-*tetramethoxy*-3-*phenylcoumarin* in needles, m. p. 210—212°, from alcohol (Found: C, 64·1; H, 5·5; OMe, 34·45. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0; 4OMe, 34·6%), forming an *acetate*, silky needles, m. p. 203—205°, from alcohol (Found: C, 62·0; H, 4·9. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

2 : 4-*Dihydroxy*-6-*methoxyphenyl* 2 : 4-*dimethoxybenzyl ketone* (Hoesch method) separated from dilute methanol in plates, m. p. 169—171°, with a wine-red ferric reaction (Found: C, 63·8; H, 5·8. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7%) and gave **4 : 7-*dihydroxy*-5 : 2′ : 4′-*trimethoxy*-3-*phenylcoumarin*** in prisms, m. p. 272—273°, from alcohol (Found: C, 63·1; H, 4·9. $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%), which yielded a *diacetate* in needles, m. p. 229—230°, from alcohol (Found: C, 61·8; H, 4·4. $C_{22}H_{20}O_9$ requires C, 61·7; H, 4·7%).

4 : 5 : 7-*Trihydroxy*-2′ : 4′-*dimethoxy*-3-*phenylcoumarin*, from 2 : 4-dimethoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone, formed needles, m. p. 305—307°, from alcohol (Found: C, 61·5; H, 4·3. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·3%), giving a *triacetate* in needles, m. p. 223—224°, from the same solvent (Found: C, 60·9; H, 4·1. $C_{23}H_{20}O_{10}$ requires C, 60·5; H, 4·4%).

4-*Hydroxy*-5 : 7 : 3′ : 4′-*tetramethoxy*-3-*phenylcoumarin*.—Prepared from phloroglucinol and 3 : 4-dimethoxybenzyl cyanide, **3 : 4-*dimethoxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone*** separated from dilute methanol in prisms, m. p. 184—186°, with a deep wine-red ferric reaction (Found:

C, 63·4; H, 5·5. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%), and with methyl sulphate–potassium carbonate gave rise to 3 : 4-*dimethoxybenzyl* 2-*hydroxy*-4 : 6-*dimethoxyphenyl ketone* in needles (80%), m. p. 101—103°, from methanol, with the same ferric reaction (Found: C, 65·4; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·1%). This ketone furnished 4-*hydroxy*-5 : 7 : 3′ : 4′-*tetramethoxy*-3-*phenylcoumarin* in long needles, m. p. 200—202°, from alcohol (Found: C, 63·65; H, 5·1; OMe, 32·4. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1; 4OMe, 34·6%), giving an *acetate* in prismatic needles, m. p. 184—185°, from alcohol (Found: C, 62·7; H, 5·3. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

2 : 4-*Dihydroxy*-6-*methoxyphenyl* 3 : 4-*dimethoxybenzyl ketone* (Hoesch reaction) formed prisms, m. p. 179—180°, from ethyl acetate–benzene, with a wine-red ferric reaction (Found: C, 64·2; H, 5·7. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7%) and gave 4 : 7-*dihydroxy*-5 : 3′ : 4′-*trimethoxy*-3-*phenylcoumarin*, needles, m. p. 262—265°, from alcohol (Found: C, 62·6; H, 4·5. $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%), forming a *diacetate* in needles, m. p. 238—240°, from alcohol (Found: C, 61·7; H, 4·4. $C_{22}H_{20}O_9$ requires C, 61·7; H, 4·7%).

4 : 5 : 7-*Trihydroxy*-3′ : 4′-*dimethoxy*-3-*phenylcoumarin*, from 3 : 4-dimethoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone, slender needles, m. p. 298—299°, from dilute alcohol (Found: C, 61·6; H, 4·5. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·3%), gave a *triacetate*, in long needles, m. p. 218—220°, from the same solvent (Found: C, 60·8; H, 3·7. $C_{23}H_{20}O_{10}$ requires C, 60·5; H, 4·4%).

4-*Hydroxy*-5 : 7-*dimethoxy*-3′ : 4′-*methylenedioxy*-3-*phenylcoumarin*.—From 3 : 4-methylenedioxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (3 g.) by the methyl sulphate–potassium carbonate method, 2-*hydroxy*-4 : 6-*dimethoxyphenyl* 3 : 4-*methylenedioxybenzyl ketone* formed plates, m. p. 98—99°, from methanol with a brown ferric reaction (Found: C, 64·5; H, 4·9; OMe, 19·6. $C_{17}H_{16}O_6$ requires C, 64·55; H, 5·1; OMe, 19·6%) and gave the *coumarin*, in prismatic needles, m. p. 234—235° (Found: C, 63·0; H, 4·2; 2OMe, 17·9. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1. OMe, 18·1%), forming an *acetate* in needles, m. p. 188—189°, from alcohol (Found: C, 62·6; H, 4·3. $C_{20}H_{16}O_8$ requires C, 62·5; H, 4·2%).

2 : 4-*Dihydroxy*-6-*methoxyphenyl* 3 : 4-*methylenedioxybenzyl ketone* (Hoesch method) separated from methanol in long plates, m. p. 143—144°, with a red ferric reaction (Found: C, 63·5; H, 4·7; OMe, 10·5. $C_{15}H_{11}O_5$·OMe requires C, 63·6; H, 4·6; OMe, 10·3%), and gave 4 : 7-*dihydroxy*-5-*methoxy*-3′ : 4′-*methylenedioxy*-3-*phenylcoumarin* in needles, m. p. 281—283°, from alcohol (Found: C, 61·9; H, 3·8. $C_{17}H_{12}O_7$ requires C, 62·2; H, 3·7%), forming a *diacetate*, needles, m. p. 218—220°, from the same solvent (Found: C, 60·9; H 4·2. $C_{21}H_{16}O_9$ requires C, 61·2; H, 3·9%).

4 : 5 : 7-*Trihydroxy*-3′ : 4′-*methylenedioxy*-3-*phenylcoumarin*, from 3 : 4-methylenedioxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone, long needles, m. p. >330°, from alcohol (Found: C, 60·9; H, 3·5. $C_{16}H_{10}O_7$ requires C, 61·15; H, 3·2%), gave a *triacetate* in rosettes of prisms, m. p. 216—218°, from the same solvent (Found: C, 60·3; H, 4·1. $C_{22}H_{16}O_{10}$ requires C, 60·0; H, 3·7%).

4 : 5 : 7-*Trihydroxy*-3-*methylcoumarin*, from phloropropiophenone, small needles, m. p. 288—290°, from dilute alcohol (Found: C, 67·5; H, 3·9. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%), yielded a *triacetate*, long needles, m. p. 180—182°, from alcohol (Found: C, 57·8; H, 4·3. $C_{16}H_{14}O_8$ requires C, 57·5; H, 4·2%).

2 : 3-*Dihydro*-5 : 7 : 4′-*trimethoxy*isoflavone.—5 : 7 : 4′-Trimethoxyisoflavone was prepared from 6-hydroxy-2 : 4-dimethoxyphenyl 4-methoxybenzyl ketone (5 g.) in ethyl formate (80 ml.) at <0° with pulverised sodium (2·5 g.) during 24 hr. On isolation in the usual manner the product was purified by chromatography from benzene on aluminium oxide (eluted with methanol–benzene, 1 : 19) and then by crystallisation from alcohol, forming plates (4·1 g.), m. p. 163—165° (cf. Baker and Robinson [7]).

Hydrogenation of this isoflavone (0·5 g.) in methanol (200 ml.) with a palladium–charcoal catalyst (from 0·5 g. of charcoal and 20 ml. of 1% palladium chloride solution) gave 2 : 3-*dihydro*-5 : 7 : 4′-*trimethoxy*isoflavone which separated from aqueous methanol in colourless plates (0·4 g.), m. p. 154—155; admixed with parent isoflavone it had m. p. 123—146° (Found: C, 68·6; H, 5·9. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). With chromic acid in acetic acid the dihydro-compound regenerated the parent isoflavone, m. p. and mixed m. p. 163—165°.

ORGANIC CHEMISTRY DEPARTMENT,
THE UNIVERSITY, LIVERPOOL.

[*Received, March 30th*, 1957.]

[7] Baker and Robinson, *J.*, 1926, 2716.

XUM

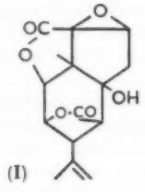
738. *Picrotoxin. Part V.**

By J. S. E. Holker, K. U. Holker, A. McGookin, Alexander Robertson, K. Sargeant, and (in part) D. E. Hathway.

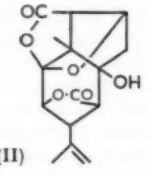
Reduction of picrotoxinin with lithium aluminium hydride gave two products which have been inter-related by oxidation with periodic acid. Similar transformations of α-dihydropicrotoxinin and picrotin have been carried out and direct structural relations established for the reduction products. The resulting evidence is discussed with particular reference to the structures (I), (II), and (III) which other workers [1,2] have put forward for picrotoxinin.

The reduction of picrotoxinin, β-bromopicrotoxinin, and β-bromopicrotoxinic acid and its ester with lithium aluminium hydride has recently been described by Johns, Slater, and Woods [1] who on the basis of their results have tentatively modified the structure (I) for picrotoxinin proposed by Conroy [3] to (II) or (III). In continuation of earlier work * an investigation on the reduction of picrotoxinin and picrotin with the same reagent, which was initiated in these laboratories in 1950, appears to be somewhat more extensive than that of Johns *et al.* and the interpretation of the results differs considerably from theirs.

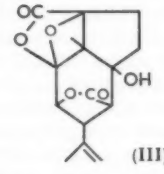
With this reagent we have found that picrotoxinin ($C_{15}H_{16}O_6$) gave a mixture of two water-soluble compounds $C_{15}H_{20}O_6$ and $C_{15}H_{22}O_6$ in 30% and 3% yield, designated



(I)



(II)



(III)

compound A and compound B respectively. The infrared absorption spectra of (A) and (B) measured in mineral oil mull were similar and both showed bands between 3550 and 3300 cm.$^{-1}$ (OH), a band at 1650 cm.$^{-1}$ (double bond of the *iso*propenyl system), and a total absence of absorption between 1850 and 1700 cm.$^{-1}$, indicating an absence of carbonyl functions.

Compound A showed some acidic properties and it could not be extracted with solvents from dilute aqueous sodium hydroxide. It formed a monomethyl ether ($C_{16}H_{22}O_6$) on treatment with dimethyl sulphate and sodium hydroxide, a diacetyl derivative ($C_{19}H_{24}O_8$), a 2 : 4-dinitrophenylhydrazone ($C_{21}H_{24}O_9N_4$), and a dihydro-derivative ($C_{15}H_{22}O_6$) on hydrogenation in the presence of Adams catalyst. Dihydro-compound A also showed some acidic properties and formed a monomethyl ether ($C_{16}H_{24}O_6$), a diacetyl derivative ($C_{19}H_{26}O_8$), and a 2 : 4-dinitrophenylhydrazone ($C_{21}H_{26}O_9N_4$). By the Zerewitinoff method compound A and its dihydro-derivative appear each to contain three active hydrogen atoms. The dihydro-derivative of compound A monomethyl ether was also formed by hydrogenation of compound A monomethyl ether with an Adams catalyst. The monomethyl ethers of compound A and its dihydro-derivative, which do not show acidic properties and cannot be acetylated even under drastic conditions, formed mono-2 : 4-dinitrophenylhydrazones identical with the respective hydrazones from compound A and its dihydro-derivative, reactions involving the demethylation of the ethers under the acidic conditions employed. This was confirmed by the hydrolysis of dihydro-compound A

* Part IV, *J.*, 1939, 1261.

[1] Johns, Slater, and Woods, *J.*, 1956, 4715.
[2] Conroy, *J. Amer. Chem. Soc.*, 1951, **73**, 1889.
[3] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 128.

monomethyl ether with acid to give dihydro-compound A in high yield. The reduction of α-dihydropicrotoxinin with lithium aluminium hydride gave dihydro-compound A, but a product corresponding to compound B was not isolated.

In view of the complete absence of carbonyl bands in the infrared absorption spectra of compound A, dihydro-compound A, and their respective methyl ethers, the formation of 2 : 4-dinitrophenylhydrazones can only be explained on the assumption that these compounds contain a system which generates an aldehydic or ketonic group under the acid conditions occurring in the preparation of the 2 : 4-dinitrophenylhydrazone, a conclusion in accordance with our inability to prepare semicarbazones of these compounds under the usual slightly alkaline conditions. These results, together with the ready formation and acid fission of the monomethyl ethers of compound A and its dihydro-derivative, are readily explained on the view that these products contain the hemiacetal system $\geq$C(OH)·O· and the monomethyl ethers the acetal system $\geq$C(OMe)·O·. The formation of the diacetate of compound A under conditions in which picrotoxinin is not acetylated implies that, in addition to that of the hemiacetal system, a second hydroxyl group has been generated in the reduction with lithium aluminium hydride.

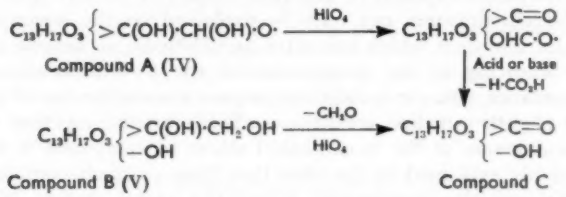
Compound B formed a diacetate ($C_{19}H_{26}O_8$) but did not show acidic properties; it did not form a methyl ether or a 2 : 4-dinitrophenylhydrazone. By the Zerewitinoff method, it appeared to contain four active hydrogen atoms.

Compound A and dihydro-compound A reacted with one molecular equivalent of periodic acid, giving products $C_{15}H_{18}O_6$ and $C_{15}H_{20}O_6$ respectively. Since these derivatives could not be acetylated it appears reasonably certain that the two hydroxyl groups of compound A and dihydro-compound A, which can be acetylated, have been destroyed in the oxidation and consequently are probably present in an α-glycol residue. On hydrogenation the oxidation product from compound A gave a dihydro-derivative identical with the oxidation product from dihydro-compound A. Further, each oxidation product gave positive hydroxamic acid tests for esters and on mild acid or alkaline hydrolysis generated formic acid together with the corresponding deformyl derivative, $C_{14}H_{18}O_5$ and $C_{14}H_{20}O_5$ respectively, which we have named compound C and dihydro-compound C. These products are readily reconverted into formates identical with the parent esters and similarly gave monoacetates ($C_{16}H_{20}O_6$) and ($C_{16}H_{22}O_6$) respectively; but, whereas dihydro-compound C, gave a crystalline 2 : 4-dinitrophenylhydrazone ($C_{20}H_{24}O_8N_4$), the corresponding derivative from compound C was amorphous. Compound C was also obtained along with formaldehyde by the oxidation of compound B with periodic acid; the monomethyl ether of compound A or its dihydro-derivative did not react with this reagent. It thus appears that in the oxidation products from compound A and its dihydro-derivative a ketonic carbonyl and an *O*-formyl group are generated. The infrared absorption spectra of both products $C_{15}H_{18}O_6$ and $C_{15}H_{20}O_6$ (in $CHCl_3$) show bands at 1757 and 1724 cm.$^{-1}$; in addition the product from compound A had a band at 1643 cm.$^{-1}$ (·CMe:CH_2). Compound C and dihydro-compound C (in $CHCl_3$) show a band at 1745 cm.$^{-1}$, and the former compound an additional band at 1643 cm.$^{-1}$ (·CMe:CH_2). The band at 1724 cm.$^{-1}$ exhibited by the oxidation products is due to the formate ester group, and that at 1757 cm.$^{-1}$ must be due to a ketonic group in a strained ring system.[3] The shift of this band to 1745 cm.$^{-1}$ in compound C and its dihydro-derivative is probably due to hydrogen bonding between the generated hydroxyl group and the keto-group.[4] These results are satisfactorily explained if compound A and its dihydro-derivative contain an α-hydroxy-hemiacetal system >C(OH)·CH(OH)·O·C$\leq$, and compound B the system (V). The reaction sequence may then be represented by the annexed partial formulæ.

The reduction of dihydro-compound C with lithium aluminium hydride or with hydrogen and an Adams catalyst gave a compound D, $C_{14}H_{22}O_5$, containing two additional hydrogen atoms and presumably arising by reduction of the keto- to a hydroxyl group. In agreement with this, compound D formed a diacetate ($C_{18}H_{26}O_7$) whereas dihydro-compound C

[4] Grove and Willis, *J.*, 1951, 877.

formed a monoacetate and, further, compound D did not show absorption in the carbonyl region of the infrared spectrum. With hydrogen and an Adams catalyst compound C absorbed two mols. of hydrogen, giving compound D, a reaction presumably involving saturation of the *iso*propenyl system in conjunction with the reduction of the keto-group.

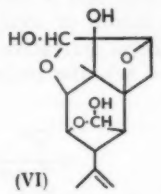


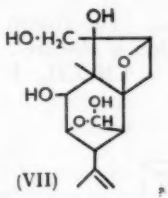
The reduction of compound C with lithium aluminium hydride furnished a product which is isomeric with dihydro-compound C, and apparently arising by reduction of the keto-group since on saturation of the *iso*propenyl group by catalytic hydrogenation this gave compound D.

The formation of an α-hydroxy-hemiacetal system (IV) in compound A and dihydro-compound A, and of the triol system (V) in compound B, seems to be best explained on the assumption that picrotoxinin and α-dihydropicrotoxinin contain an α-hydroxy-lactone or potential α-hydroxy-lactone system which undergoes reduction. Reduction of a lactone to a hemiacetal has been previously observed [5] in certain cases where a limited amount of lithium aluminium hydride has been employed. The isolation of an intermediate reduction product from picrotoxinin with an excess of lithium aluminium hydride is unusual but can be explained on the assumption that compound A is precipitated as an insoluble metallic complex and thus is preserved from further reaction. The reduction of the lactone system envisaged in the formation of compounds A and B only requires a hydrogen increment of two and four atoms respectively, whereas the compounds differ from the parent by four and six atoms respectively. Hence it appears that in the production of compound A and B a second function present in picrotoxinin must also have been reduced, involving the addition of two more hydrogen atoms. The nature of this second reducible function in picrotoxinin is less clear, but if the compound has a dilactone structure both lactone rings must be reduced in the formation of compound A and B, and, from the composition and nature of the products, reduction of the second lactone ring must be confined to the addition of two hydrogen atoms, *i.e.*, formation of a hemiacetal system would normally be expected. It has proved impossible to obtain direct evidence for the presence of this system in our transformation products. Thus by its method of preparation, dihydro-compound C, should still contain the second hemiacetal system together with a ketonic function and an alcoholic hydroxyl group. It forms only a monoacetate, showing infrared bands (in $CHCl_3$) at 1739 (*O*-acetate) and 1757 cm.$^{-1}$ (keto-group in a strained ring system) and a doublet at 3597 and 3425 cm.$^{-1}$, indicating that this compound still contains a hydroxyl group which may be present in a hemiacetal system. Many attempts were made to isolate an oxidation product from dihydro-compound C acetate containing a lactone ring regenerated by the oxidation of the hemiacetal system but, although the acetate readily consumed chromic oxide, the only homogeneous product isolated was unchanged starting material. Thus it appears that the oxidation products formed undergo further degradation more readily than the original compound. On the other hand, with chromic acid dihydro-compound C gave a product $C_{14}H_{18}O_5$ which apparently arises by oxidation of the secondary alcoholic hydroxyl group to a keto-group. In support of this conclusion the infrared spectrum of the oxidation product shows bands (in $CHCl_3$) at 1760 (keto-group in strained ring system) and 1718 cm.$^{-1}$ (attributed to the second keto-group formed in the oxidation and probably present in a

[5] Arth, *J. Amer. Chem. Soc.*, 1953, **75**, 2413; Hinder and Stoll, *Helv. Chim. Acta*, 1954, **37**, 1866.

six-membered ring) and a doublet at 3600 and 3450 cm.$^{-1}$ (hydroxyl). Therefore, the presence of a hemiacetal system in these compounds seems unlikely. Nevertheless, attempts were made to accommodate the foregoing reactions on the basis of the Conroy structure (I) for picrotoxinin on the assumption that in the formation of compound A the reduction of both lactone rings to hemiacetal systems is accompanied by a 1 : 2-epoxide–ether rearrangement. Compounds A and B would then have structures of the type (VI) and (VII) respectively.


(VI)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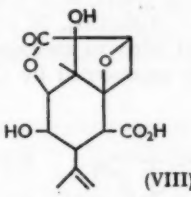
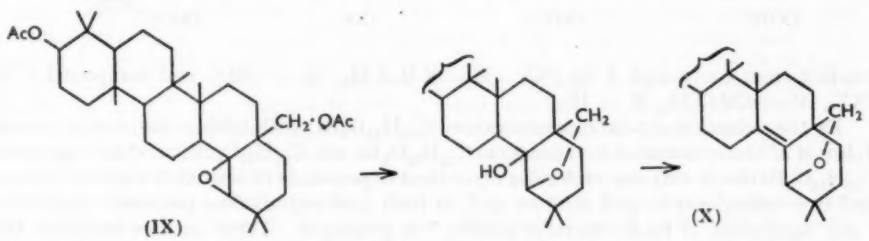
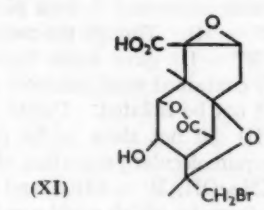

(VIII)

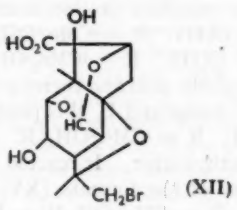
A similar rearrangement of a 1 : 2-epoxide to an ether in a lithium aluminium hydride reduction has been postulated [6] to explain the formation of compound (X) from moradiol diacetate oxide (IX); to account for the properties of picrotoxic acid Benstead *et al.*[7] have


(IX) (X)

suggested that it had structure (VIII) and that its formation from picrotoxinin involves epoxide–ether rearrangement.

After this communication * had been drafted and originally submitted for publication, a paper by Conroy [8] became available in which the reduction product of β-bromopicrotoxinic acid (XI) with sodium borohydride was shown to be an α-hydroxy-acid. On mechanistic grounds the structure (XII) was advanced for this product. This is attractive


(XI)


(XII)

because it explains the reduction of the lactone ring of β-bromopicrotoxinic acid by the addition of two hydrogen atoms without the formation of a hemiacetal system. Similarly,

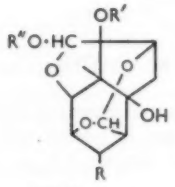
* In place of structure (VI), one of us (J. S. E. H.) originally considered that of three alternatives structure (XIII; R = $\cdot$CMe:CH$_2$, R′ = R″ = H) was possible for the reduction product. Following the paper by Dr. H. Conroy [8] this possibility, which was suggested independently by a referee, became more attractive.—A. R.

[6] Barton and Brooks, *J.*, 1951, 257.
[7] Benstead, Gee, Johns, Martin Smith, and Slater, *J.*, 1952, 2292.
[8] Conroy, *J. Amer. Chem. Soc.*, 1957, **79**, 1726.

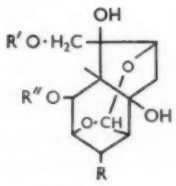
the foregoing reduction of picrotoxinin may be explained satisfactorily on the assumption that the formation of compounds A and B proceeds by a parallel route.

Thus it appears that (XIII; R = ·CMe:CH_2, R′ = R″ = H) and (XIV; R = ·CMe:CH_2, R′ = R″ = H) are more acceptable formulations of compound A and B respectively than formulæ (VI) and (VII).

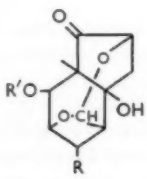
The acidic properties of compound A are considered to be due to the hemiacetal hydroxyl group of the α-hydroxy-hemiacetal system and accordingly the momomethyl ether is formulated as (XIII, R = ·CMe:CH_2, R′ = H, R″ = Me) and compound A diacetate as (XIII; R = ·CMe:CH_2, R′ = R″ = Ac). The reason for the failure of compound A monomethyl ether to undergo acetylation is obscure. The diacetyl derivative of compound B is represented by (XIV; R = ·CMe:CH_2, R′ = R″ = Ac), the periodic acid



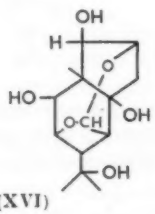
(XIII)



(XIV)



(XV)



(XVI)

product from compound A by (XV; R = ·CMe:CH_2, R′ = CHO), and compound C by (XV; R = ·CMe:CH_2, R′ = H).

By the reduction of β-bromopicrotoxinin ($C_{15}H_{15}O_6Br$) with lithium aluminium hydride Johns *et al.*[1] have obtained two products $C_{15}H_{23}O_6Br$ and $C_{15}H_{21}O_6Br$, of which compound $C_{15}H_{23}O_6Br$ reacts with one molecular equivalent of periodate in neutral or alkaline solution and two equivalents in acid solution and, in both acid and alkaline periodate oxidations, " one equivalent of back-titratable acidity " is produced. These authors attribute this acidity to the formation of a lactone ring in the oxidation product, but in view of the present results the acidity is in all probability due to a formate ester group and therefore structures (II) and (III) for picrotoxinin, which are based on the presence of a lactone ring in this periodate product, do not merit further consideration at this stage.

In an examination of the reduction of picrotin ($C_{15}H_{18}O_7$) with lithium aluminium hydride a water-soluble compound ($C_{15}H_{22}O_7$) was obtained which formed a 2 : 4-dinitrophenylhydrazone and a diacetate ($C_{19}H_{26}O_9$) under conditions in which picrotin is not acetylated. This reduction product corresponds with compound A from picrotoxinin and is formulated as (XIII; R = ·CMe_2·OH, R′ = R″ = H). Though the residues left after the isolation of (XIII; R = ·CMe_2·OH, R′ = R″ = H) gave some formaldehyde on oxidation with periodic acid and therefore probably contained small amounts of a substance corresponding to compound B, this product could not be isolated. Unlike compound A, compound (XIII; R = ·CMe_2·OH, R′ = R″ = H) did not show acidic properties and did not give a methyl ether. It reacted with an equimolecular proportion of periodic acid to give a mixture of the formate (XV; R = ·CMe_2·OH, R′ = CHO) and the deformyl compound (XV; R = ·CMe_2·OH, R′ = H). The formate, which could not be acetylated, was readily hydrolysed to the deformyl compound, which, like compound C, yielded a monoacetate (XV; R = ·CMe_2·OH, R′ = Ac) and a 2 : 4-dinitrophenylhydrazone.

A direct relationship has been established between compound C of the picrotoxinin series and compound (XV; R = ·CMe_2·OH, R′ = H) derived from picrotin, confirming the earlier evidence for the structural similarity of picrotoxinin and picrotin. Thus, treatment of compound C with perbenzoic acid gave an epoxide which was not isolated but subjected immediately to reduction with lithium aluminium hydride, giving a compound ($C_{14}H_{22}O_6$) formulated as (XVI). This product, which was formed from compound (XV;

XUM

R = ·CMe_2·OH, R′ = H) by reduction with lithium aluminium hydride or by hydrogenation in the presence of a Raney nickel catalyst, surprisingly formed a triacetate.

Although the work described in this paper can be rationally explained on the Conroy picrotoxinin formulation it does not necessarily exclude other possible structures and further work is in progress.

Experimental

Unless stated otherwise optical rotations were measured in EtOH at room temperature (18—22°) with a 1-dm. tube, ultraviolet absorption spectra in 95% EtOH with a Unicam spectrophotometer, and infrared spectra with a Perkin-Elmer model 21 double-beam spectrophotometer.

The light petroleum employed had b. p. 60—80°.

Reduction of Picrotoxinin.—A solution of lithium aluminium hydride (5 g.) in ether (500 ml.) was heated under reflux in the boiling flask of a Soxhlet apparatus, the thimble of which contained picrotoxinin (10 g.). 24 Hr. later the extraction was complete and, after the destruction of the excess of lithium aluminium hydride with methanol (20 ml.) in ether (150 ml.), ice (100 g.) and 2N-sulphuric acid (300 ml.) were added to the stirred mixture. The ether layer was separated, the aqueous phase was continuously extracted with ether for 20 hr., and the combined ether extracts were concentrated (50 ml.), diluted with ethyl acetate (600 ml.), dried ($MgSO_4$), and again concentrated (20 ml.). On being kept for several weeks the solution deposited colourless crystals (4·6 g.), m. p. 185—195°. The mother-liquors contained only intractable gum (3·7 g.). Repeated recrystallisation of the crystalline product from ethyl acetate gave compound A (XIII; R = ·CMe:CH_2, R′ = R″ = H) in hard rhombs (3·3 g.), m. p. 209—211°, $[\alpha]_D$ −29° (*c* 1·60) (Found: C, 60·7; H, 7·0; active H, 1·06. Calc. for $C_{15}H_{20}O_6$: C, 60·8; H, 6·8; 3 active H, 1·02%), which appears to be identical with the compound $C_{15}H_{20}O_6$, m. p. 212°, isolated by Johns *et al.*[1] Prepared by acetic anhydride–pyridine, the *diacetate* (XIII; R = ·CMe:CH_2, R′ = R″ = Ac) separated from benzene in thin plates, m. p. 213—214° (Found: C, 60·1; H, 6·4; Ac, 19·1. $C_{15}H_{18}O_6Ac_2$ requires C, 60·0; H, 6·4; Ac, 22·6%). The mother-liquors from A were evaporated and, after being extracted with boiling chloroform (5 × 25 ml.), the residue was crystallised from the same solvent, giving *compound* B (XIV; R = ·CMe:CH_2, R′ = R″ = H) in needles, m. p. 214—216°, which then formed hard rods (0·3 g.), m. p. 212—214° (from ethyl acetate–benzene), $[\alpha]_D$ −53° (*c* 1·11) (Found: C, 60·8; H, 7·2; active H, 1·3. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4; 4 active H, 1·3%), mixed m. p. with compound A, 185—195°, The *diacetate* (XIV; R = ·CMe:CH_2, R′ = R″ = Ac) separated from benzene–light petroleum in needles, m. p. 160—162° (Found: C, 59·6; H, 6·7; Ac, 23·9. $C_{15}H_{18}O_6Ac_2$ requires C, 59·7; H, 6·8; Ac, 22·5%). Prepared with a solution of 2 : 4-dinitrophenylhydrazine sulphate in 6N-sulphuric acid, the *dinitrophenylhydrazone* of compound A separated from ethanol in yellow needles, m. p. 298—300° (decomp.) (Found: C, 52·9; H, 5·3; N, 11·7. $C_{21}H_{24}O_9N_4$ requires C, 52·9; H, 5·1; N, 11·8%).

Prepared by methyl sulphate–aqueous sodium hydroxide, the monomethyl ether (XIII; R = ·CMe:CH_2, R′ = H, R″ = Me) of compound A separated from benzene–light petroleum in needles, m. p. 170—171°, $[\alpha]_D$ +12° (*c* 2·38) (Found: C, 62·0; H, 7·2; OMe, 10·2. Calc. for $C_{16}H_{22}O_6$: C, 61·9; H, 7·2; OMe, 10·0%) (cf. Johns *et al.*[1] who give m. p. 170° for the ether prepared by this method and m. p. 176° for derivative prepared with diazomethane). With 2 : 4-dinitrophenylhydrazine sulphate in 8N-sulphuric acid the ether gave the 2 : 4-dinitrophenylhydrazone of compound A, separating from alcohol in yellow needles, m. p. and mixed m. p. 298—300° (decomp.) (Found: C, 52·8; H, 5·1; N, 11·7%; OMe, 0). This ether was recovered unchanged after treatment with (*a*) acetic anhydride and fused sodium acetate at the reflux temperature for 3 hr., (*b*) lithium aluminium hydride, (*c*) periodic acid, or (*d*) 10% aqueous potassium hydroxide at 100° for 3 hr.

Dihydro-compound A (XIII; R = ·$CHMe_2$, R′ = R″ = H).—α-Dihydropictotoxinin (10 g.) was reduced with lithium aluminium hydride (5 g.) by the procedure employed for picrotoxinin, and the gummy product (8·5 g.) was repeatedly recrystallised from benzene–ethyl acetate, giving dihydro-compound A in felted needles (3·2 g.), m. p. and mixed m. p. 209—211°, $[\alpha]_D$ −9·0° (*c* 1·43), identical with a specimen prepared by the reduction of compound A with hydrogen and a platinum catalyst (cf. Johns *et al.*[1] who do not give a m. p.) (Found: C, 60·4; H, 7·4; active H, 0·98. Calc. for $C_{15}H_{22}O_6$: C, 60·4; H, 7·4; 3 active H, 1·01%). The

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mother-liquors contained only intractable gum. The *diacetate* (XIII; R = ·CHMe$_2$, R′ = R″ = Ac) separated from benzene–carbon tetrachloride in plates, m. p. 216—218° (Found: C, 59·6; H, 6·7; Ac, 19·1. $C_{19}H_{26}O_8$ requires C, 59·7; H, 6·8; Ac, 22·5%). The 2 : 4-dinitrophenylhydrazone was obtained as an amorphous yellow solid.

Methyl Ether of Dihydro-compound A (XIII; R = CHMe$_2$, R′ = H, R″ = Me).—Dihydro-compound A was methylated with dimethyl sulphate and sodium hydroxide, to give the *methyl ether* which separated from benzene–light petroleum in needles, m. p. 179—180°, $[\alpha]_D$ + 28° (*c* 1·08) (Found: C, 61·6; H, 7·4; OMe, 10·2. $C_{16}H_{24}O_6$ requires C, 61·5; H, 7·7; OMe, 10·0%).

On reduction in alcohol with hydrogen (approx. 1 mol. absorbed) and a platinum catalyst the methyl ether of compound A gave a theoretical yield of the dihydro-derivative which formed needles, m. p. and mixed m. p. 179—180°, $[\alpha]_D$ +28° (*c* 3·77), from benzene–light petroleum (Found; OMe, 9·9%). Treatment of this ether with 2 : 4-dinitrophenylhydrazine sulphate in 8N-sulphuric acid gave an amorphous, yellow 2 : 4-dinitrophenylhydrazone. The ether was recovered unchanged after being heated with boiling acetic anhydride and fused sodium acetate for 3 hr. or methyl iodide and silver oxide for 48 hr.

The ether (0·5 g.) was shaken with 2N-hydrochloric acid (50 ml.) at room temperature until dissolution was complete (24 hr.) and the resulting dihydro-compound A isolated with ether and crystallised from chloroform, forming felted needles (0·3 g.), m. p. 203—206°; admixed with an authentic specimen it had m. p. 204—208°.

Oxidation of Compound A with Periodic Acid.—Sodium periodate (4·4 g.) in water (20 ml.) and concentrated sulphuric acid (3·5 ml.) was added at 0° to a solution of compound A (4 g.) in water (60 ml.). The precipitate (3·13 g.), m. p. 162—165°, which began to separate after 30 sec. was collected 10 min. later and crystallised from benzene, giving the *product* (XV; R = ·CMe:CH$_2$, R′ = CHO) in plates or rhombs, m. p. 171—172°, $[\alpha]_D$ −121° (*c* 2·51), $\lambda_{max.}$ 309 mμ (ε 27) (Found: C, 61·4; H, 6·2; active H, 0·39. $C_{15}H_{16}O_6$ requires C, 61·2; H, 6·2; 1 active H, 0·34%). This compound gave a positive hydroxamic acid test for an ester and it was recovered unchanged after treatment with semicarbazide hydrochloride and sodium acetate in aqueous solution or with acetic anhydride and pyridine.

A solution of this oxidation product (2 g.) in 1% aqueous sodium hydroxide (35 ml.) was kept at room temperature for 2 days and then repeatedly extracted with ether. The dried ethereal solution was evaporated, leaving a colourless residue (1·71 g.), m. p. 170°, which on crystallisation from benzene gave *compound* C (XV; R = ·CMe:CH$_2$, R′ = H) in plates, m. p. 171—172°, $[\alpha]_D$ −178° (*c* 4·03), $\lambda_{max.}$ 312 mμ (ε 37); admixed with the parent compound it had m. p. 145—150° (Found: C, 63·1; H, 6·8; active H, 0·81. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8; 2 active H, 0·75%). The concentrated residual alkaline liquors (10 ml.) were acidified with hydrochloric acid (5 ml.), and the formic acid present was characterised by conversion into benziminazole (0·49 g., 60%), m. p. and mixed m. p. 169—170°, giving the picrate, m. p. and mixed m. p. 225—226°, according to the method of Brown and Campbell.[•] Compound C gave a *monoacetate* (XV; R = ·CMe:CH$_2$, R′ = Ac) which separated from benzene in needles, m. p. 205—206° (Found: C, 62·3; H, 6·5; Ac, 13·9. $C_{16}H_{20}O_6$ requires C, 62·4; H, 6·6; Ac, 14·0%), and an amorphous yellow 2 : 4-dinitrophenylhydrazone.

Oxidation of Dihydro-compound A with Periodic Acid.—Dihydro-compound A (4 g.) was oxidised with periodic acid under the conditions used for the oxidation of compound A and the *product* (XV; R = ·CHMe$_2$, R′ = CHO) (3·2 g.), m. p. 180—186°, isolated from the reaction mixture and crystallised from benzene, forming plates or rhombs (2·7 g.), m. p. 187—188°, $[\alpha]_D$ −116° (*c* 3·09), $\lambda_{max.}$ 310·5 mμ (ε, 29) (Found: C, 60·8; H, 6·8; active H, 0·41. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8; 1 active H, 0·34%). The same compound was obtained by reduction of the periodic acid oxidation product of compound A (2 g.) in alcohol with hydrogen (approx. 1 mol. absorbed) and a platinum catalyst and formed plates (1·05 g.), m. p. and mixed m. p. 187—188°, from benzene (Found: C, 61·1; H, 6·9%). The residues from the purification of this consisted of an inseparable mixture. In some (apparently identical) reduction experiments the only product isolated had m. p. 215—216·5° after purification from benzene and was later shown to be identical with compound D (see below.).

The periodic acid product from dihydro-compound A, like the corresponding product from compound A, gave a positive hydroxamic acid test for esters, and did not form an acetate or a semicarbazone.

Dihydro-compound C (XV; R = CHMe$_2$, R′ = H) (With J. H. Taylor).—The periodic acid

[•] Brown and Campbell, *J.*, 1937, 1699.

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product (2·5 g.) from compound A was hydrolysed with 1% aqueous sodium hydroxide (40 ml.) at room temperature for 2 days and the resulting *dihydro-compound C* was isolated with ether and crystallised from benzene, forming plates, m. p. 187—188°, $[\alpha]_D$ −156° (*c* 3·00), $\lambda_{max.}$ 313 mμ (ε 24) (Found: C, 62·6; H, 7·5; active H, 0·89. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5; 2 active H, 0·74%). Admixed with the oxidation product of dihydro-compound A, it had m. p. 145—150°. The formic acid produced in the hydrolysis was characterised by conversion into benziminazole, m. p. and mixed m. p. 169—170°.

On treatment with acetic anhydride, 95% formic acid, and pyridine dihydro-compound C regenerated the formate, m. p. 186—188°, identical with the periodic acid product from dihydro-compound A. It also gave a *monoacetate* (XV; R = $CHMe_2$, R′ = Ac), forming needles, m. p. 200°, from benzene (Found: C, 61·7; H, 7·2; Ac, 13·6. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1; Ac, 13·8%), and a 2 : 4-*dinitrophenylhydrazone*, orange-yellow needles from alcohol, m. p. 246—250° (decomp.) (Found: C, 53·4; H, 5·3; N, 12·3. $C_{20}H_{24}O_8N_4$ requires C, 53·6; H, 5·4; N, 12·5%). The periodic acid oxidation product from dihydro-compound A gave the same 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 246—250°, when treated with a boiling solution of 2 : 4-dinitrophenylhydrazine (0·3 g.) and hydrochloric acid (0·5 ml.) in alcohol (25 ml.).

Dihydro-compound C (5 g.), in water (125 ml.), was treated at 0° with a solution of potassium dichromate (10 g.) in 8N-sulphuric acid (65 ml.) and 2 hr. later the crystalline precipitate was collected, washed, dried, and purified from benzene–ethyl acetate, giving the oxidation *product* in large rhombs (3·7 g.), m. p. 224—228° (decomp.), $[\alpha]_D$ −81° (*c* 2·79), $\lambda_{max.}$ 311 mμ (ε 128) (Found: C, 63·4; H, 6·8. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%).

The acetate of dihydro-compound C was treated with chromic oxide in acetic acid in many experiments performed under different conditions. Although reduction of the chromic oxide occurred readily at room temperature a crystalline oxidation product was not isolated.

iso*Dihydro-compound C*.—Compound C (4 g.) was reduced with lithium aluminium hydride (3 g.) in ether (150 ml.) by the method employed for picrotoxinin, and the product (3·92 g.), m. p. 178—180°, crystallised from benzene, giving iso*dihydro-compound C* in efflorescent needles, m. p. 179—180°, $[\alpha]_D$ −49° (*c* 3·47) (Found: C, 62·7; H, 7·4; active H, 1·16. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5; 3 active H, 1·12%). The *diacetate* formed needles, m. p. 207—209°, from benzene–light petroleum (Found: C, 61·1; H, 6·7; Ac, 25·1. $C_{18}H_{24}O_7$ requires C, 61·3; H, 6·9; Ac, 24·5%).

Oxidation of Compound B with Periodic Acid.—(*a*) Sodium periodate (0·11 g.), in water (1 ml.) and sulphuric acid (2 drops), was mixed with a solution of compound B (0·1 g.) in water (2·5 ml.) at room temperature and 15 min. later the excess of periodic and iodic acid was removed by titration of the acidified solution with 0·4% sodium sulphite solution and a starch indicator. The mixture was diluted with water (60 ml.) and distilled. The formaldehyde in the distillate was characterised as the dimedone derivative (80 mg.), m. p. and mixed m. p. 188—189°. In another experiment the formaldehyde was isolated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 164° (decomp.).

(*b*) Compound B (0·5 g.), in water (20 ml.), was treated with a solution of sodium periodate (0·5 g.) in 4N-sulphuric acid (6 ml.) at room temperature and the product isolated with ether and crystallised from benzene, giving compound C in plates (0·26 g.), m. p. and mixed m. p. 171—172° (Found: C, 63·0; H, 6·9%).

Compound D.—(*a*) Dihydro-compound C (0·5 g.) was reduced with lithium aluminium hydride (1 g.) in ether, and the product (0·44 g.), m. p. 211—212°, isolated with ether and crystallised from benzene, giving *compound D* in plates, m. p. 215—216·5°, $[\alpha]_D$ −17° (*c* 3·85) (Found: C, 62·1; H, 8·4; active H, 1·02. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2; 3 active H, 1·11%).

(*b*) Hydrogenation of compound C, dihydro-compound C, or *iso*dihydro-compound C (2 mol., 1 mol., and 1 mol. of hydrogen absorbed respectively) in alcohol with platinum catalyst gave a theoretical yield of compound D, m. p. and mixed m. p. 215—216·5°. The *diacetate* formed needles (from benzene–light petroleum), m. p. 201—202° (Found: C, 60·7; H, 7·1; Ac, 24·0. $C_{18}H_{26}O_7$ requires C, 61·0; H, 7·4; Ac, 24·3%).

Reduction of Picrotin.—This compound (8 g.) was reduced with lithium aluminium hydride (5 g.) in ether (500 ml.), and the resulting sticky resin triturated with cold ethyl acetate (30 ml.) to give an insoluble white powder (3 g.). Crystallised from ethyl acetate, this gave the reduction *product* (XIII; R = ·CMe_2·OH, R′ = R″ = H) in needles (2·5 g.), m. p. 222—224°, $[\alpha]_D$ −45°

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(*c* 2·5) (Found: C, 57·5; H, 7·1. $C_{15}H_{22}O_7$ requires C, 57·3; H, 7·1%). This compound gave a *diacetate* which separated from ethyl acetate in rhombs, m. p. 242—244° (decomp.) (Found: C, 57·5; H, 6·4; Ac, 22·0. $C_{19}H_{26}O_9$ requires C, 57·3; H, 6·6; Ac, 21·6%), and a 2 : 4-*dinitrophenylhydrazone* from alcohol in yellow plates, m. p. 297—299° (decomp.) (Found: N, 11·6. $C_{21}H_{26}O_{10}N_4$ requires N, 11·3%).

Oxidation of the Foregoing Reduction Product.—(a) *With lead tetra-acetate.* A solution of the reduction product (1 g.) in acetic acid (5 ml.) was added to lead tetra-acetate (1·3 g.) in acetic acid (25 ml.), kept at room temperature for 24 hr., diluted with water (100 ml.), and neutralised with sodium hydrogen carbonate. Isolated with ether, the resulting formate (XV; R = CMe_2·OH, R′ = CHO) crystallised from acetone–light petroleum in long plates (0·6 g.), m. p. 187—189°, $[\alpha]_D$ −130° (*c* 4·7) (Found: C, 57·6; H, 6·9. $C_{15}H_{20}O_7$ requires C, 57·7; H, 6·5%).

(b) *With periodic acid.* A solution of the reduction product (4 g.) in water (15 ml.) was added to sodium periodate (5 g.) dissolved in water (10 ml.) containing sulphuric acid (60 drops) at 0° and the mixture kept at this temperature for 1 hr. The crystalline precipitate (2·5 g.), which on being heated melted at 80°, solidified, and then melted at 175—180°, was dehydrated at 100° and then crystallised from acetone–light petroleum, to give the formate in long plates (2 g.), m. p. and mixed m. p. 187—189° (Found: C, 57·5; H, 6·4%).

The residual aqueous solution left after the isolation of the formate was extracted into ether (5 × 50 ml.), and the extract washed with aqueous sodium hydrogen carbonate and dried (Na_2SO_4). Evaporation of the solvent left a white residue (1·5 g.) of the *deformyl compound* (XV; R = CMe_2·OH, R′ = H) which separated from acetone–light petroleum in cubes or from benzene–ethyl acetate in plates, m. p. 224—226°, $[\alpha]_D$ −175° (*c* 4·0) (Found: C, 59·2; H, 7·2. $C_{14}H_{20}O_6$ requires C, 59·1; H, 7·1%). The same compound was obtained by hydrolysis of the formate (0·2 g.) with sulphuric acid (15 drops) in water (20 ml.) at 0° for 24 hr. or with potassium hydroxide (0·2 g.) in water (7 ml.) at 0° for 1 hr. The production of formic acid in the hydrolysis of the oxidation product, m. p. 187—189° with 2N-sulphuric acid was established by isolation and conversion of the formic acid into benziminazole (yield, 47% of the theoretical for one formate residue). The deformyl compound, m. p. 224—226°, gave a *monoacetate* (XV; R = CMe_2·OH, R′ = Ac), forming needles, m. p. 222—223°, from acetone–light petroleum (Found: C, 59·2; H, 7·0; Ac, 15·8. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8; Ac, 13·1%), and a 2 : 4-*dinitrophenylhydrazone*, yellow flakes, m. p. 278—280° (decomp.), from benzene–ethyl acetate (Found: C, 52·1; H, 5·1; N, 12·3. $C_{20}H_{24}O_9N_4$ requires C, 51·7; H, 5·1; N, 12·1%). The formate (XV; R = CMe_2·OH, R′ = CHO) gave the same 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 278—280° (decomp.) (Found: N, 12·1%), presumably by initial hydrolysis of the formate group by the acidic reagent.

Relationship between the Picrotoxinin and Picrotin Transformation Products.—(*a*) The deformyl compound (0·5 g.) derived from picrotin was reduced with lithium aluminium hydride (0·5 g.) in ether (100 ml.), and the product isolated by continuous extraction with ether and crystallised from benzene, giving the reduction *product* (XVI) in needles (0·3 g.), m. p. 80° (decomp.), resolidifying, and finally melting at 188—190°. Dried in a vacuum at 100° the compound had m. p. 188—190°, $[\alpha]_D$ −46° (*c* 2·6) (Found: C, 58·6; H, 7·9. $C_{14}H_{22}O_6$ requires C, 58·7; H, 7·8%). The same reduction product was formed by the hydrogenation of the deformyl compound (0·5 g.) in the presence of a Raney nickel (W. 7) catalyst, with an identical infrared absorption spectrum.

(*b*) Compound C (3·1 g.) from picrotoxinin was added to a solution of perbenzoic acid (2 mol. equivs.) in chloroform (100 ml.), and the mixture was kept in the dark at 0° for 48 hr., and filtered through a column of aluminium oxide (1 × 18 cm.) which was then washed with chloroform (100 ml.). Evaporation of the combined filtrate and washings left a gum which was reduced with lithium aluminium hydride (3 g.) in ether (100 ml.) by the continuous-extraction procedure. The product (1·8 g.) was isolated in ether and repeatedly crystallised from benzene, giving the compound, m. p. 188—190°, $[\alpha]_D$ −47° (*c* 2·82) (Found: C, 58·8; H, 7·6%), shown to be identical with the reduction compound (XVI) by mixed m. p. and by comparison of the infrared absorption spectra. The compound gave a *triacetate*, which separated from benzene–light petroleum in rhombs, m. p. 197—198° (Found: C, 58·2; H, 6·7; Ac, 31·4. $C_{20}H_{28}O_9$ requires C, 58·2; H, 6·9; Ac, 31·4%).

UNIVERSITY OF LIVERPOOL.

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739. *Hydrogenolysis of Aromatic Carbonyl Compounds and Alcohols with Aluminium Chloride and Lithium Aluminium Hydride.*

By B. R. Brown and A. M. S. White.

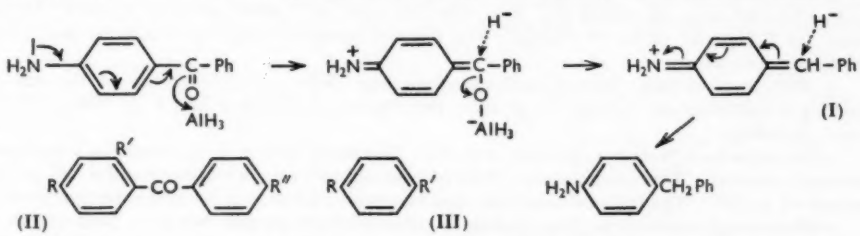
Aromatic ketones are smoothly hydrogenolysed by aluminium chloride and lithium aluminium hydride in ether. Benzaldehyde yields benzyl alcohol, but *p*-methoxy- and *p*-dimethylamino-benzaldehyde give the corresponding toluenes. These effects are interpreted as the result of the reduction of an intermediate carbonium ion.

The hydrogenolysis of amides ($NR_2{\cdot}COR' \longrightarrow NR_2{\cdot}CH_2R'$) and vinylogues of amides with lithium aluminium hydride has been extended to substituted aromatic carbonyl compounds by Conover and Tarbell [1] who used excess of lithium aluminium hydride at up to 90° for several days, obtaining yields of 30—80%. A mechanism was proposed, similar to that for amides,[2] the essential feature of which is the production and reduction of a

$$Ar{\cdot}CHR{\cdot}OH + A \longrightarrow Ar{\cdot}CHR^+ + HOA^-$$

mesomeric cation, *e.g.*, (I). This results from the attack of a Lewis acid on an alcohol, and this ionisation would be aided by use of a stronger Lewis acid (*e.g.*, aluminium chloride), presence of electron-donating groups in the *ortho*- or *para*-position of the benzene ring, or introduction of a group R capable of facilitating ionisation.

It has been reported [3,4,5] that such hydrogenolyses of allylic alcohols are promoted by aluminium chloride in the presence of lithium aluminium hydride. We now record the hydrogenolysis of a number of aldehydes, ketones, and alcohols according to the above scheme. Thus benzophenone, a number of substituted benzophenones (II; R = R″ = NMe_2, R′ = H; R = R″ = OMe, R′ = H; R = R′ = R″ = OMe), and α-*p*-methoxyphenylbenzyl alcohol on brief treatment with aluminium chloride and lithium aluminium



hydride (2 : 1 mol.) in ether gave the corresponding diphenylmethanes in yields of about 90%, and benzanthrone gave benzanthrene. Similarly acetophenone and substituted acetophenones (III; R′ = Ac) yield ethylbenzenes. It thus appears that this is a general method for the hydrogenolysis of aryl ketones, though the use of a molar ratio of aluminium chloride to lithium aluminium hydride of less than 2 : 1 results in the production of styrene from acetophenone, presumably by reduction to the alcohol, replacement of the hydroxyl group by chlorine,[6] and loss of hydrogen chloride on distillation.[3] In contrast benzaldehyde, even with an aluminium chloride–lithium aluminium hydride ratio of 2 : 1, yields the normal lithium aluminium hydride reduction product, benzyl alcohol. Introduction of a *p*-methoxy- or *p*-dimethylamino-group, giving (III; R = OMe or

[1] Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586.
[2] Gaylord, *Experientia*, 1954, **10**, 166, 423.
[3] Broome and Brown, *Chem. and Ind.*, 1956, 1307.
[4] Birch and Slaytor, *ibid.*, p. 1524.
[5] Wheeler and Mateos, *ibid.*, 1957, 395.
[6] Cf. Broome, Brown, and Summers, *J.*, 1957, 2071.

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NMe_2, R′ = CHO), results in 90% yields of the corresponding toluenes. Thus, for aryl aldehydes a structural requisite for hydrogenolysis is a *para*-group which is capable of donating electrons to facilitate the production of, and to stabilise sufficiently, the intermediate carbonium ion.

When this paper had been written, an abstract [7] reporting similar results became available.

Experimental

Light petroleum refers to the fraction of b. p. 40—60° unless otherwise stated. References given as " lit." are from Beilstein's " Handbuch."

General Method.—The reagent was prepared by the addition of lithium aluminium hydride (1·75 mol.) to a solution of aluminium chloride (3·5 mol.) in ether (1·33 mol.). After the vigorous reaction had subsided the alcohol, aldehyde, or ketone (1 mol.) was added, as solid or in ether, during 5—10 min. Each addition produced a vigorous reaction accompanied by a transient colour (usually orange). The reaction was completed by boiling the mixture under reflux for 20—30 min. Excess of methyl formate in ether was added at 0° to decompose excess of reducing agent, and the mixture was worked up in the usual way with 20% sulphuric acid or 20% aqueous sodium hydroxide (for basic products). Evaporation of the dried ether layer yielded the crude product which was purified and characterised as described below.

Specific Examples.—Benzyl alcohol from benzaldehyde (8·3 g.). Distillation gave a colourless oil (5·1 g.), b. p. 204°/765 mm., n_D^{18} 1·5367 (lit., b. p. 205°/760 mm., n_D^{20} 1·5395). The phenylurethane had m. p. 78° (lit., 78°).

p-*Methoxytoluene from* p-*anisaldehyde* (9·68 g.). The oil, in light petroleum, was filtered through alumina. *p*-Methoxytoluene (6·75 g.) was obtained having b. p. 172—173°/753 mm., n_D^{19} 1·5124 (lit., b. p. 177°/760 mm., n_D^{19} 1·5124).

p-*Dimethylaminotoluene from* p-*dimethylaminobenzaldehyde* (8·01 g.). Distillation gave a liquid (6·54 g.), b. p. 211°/765 mm., n_D^{16} 1·5486 (lit., b. p. 211°/760 mm., n_D^{20} 1·5470). The picrate separated from alcohol as yellow needles, m. p. 130°. von Braun [8] gives m. p. 130°.

Ethylbenzene from acetophenone (8·7 g.). Distillation gave ethylbenzene (7·2 g.), b. p. 136—138°/766 mm., n_D^{17} 1·5032 (lit., b. p. 136°/760 mm., n_D^{15} 1·4986) (Found: C, 90·5; H, 9·2. Calc. for C_8H_{10}: C, 90·6; H, 9·4%). The infrared spectrum was identical with that of an authentic specimen.

p-*Methoxyethylbenzene from* p-*methoxyacetophenone* (3·98 g.). Distillation of the residue yielded a colourless oil (2·54 g.), b. p. 192—193°/742 mm., n_D^{19} 1·505 (lit., b. p. 195—196°/760 mm., n_D 1·509).

Diphenylmethane from benzophenone (4·26 g.). The residual oil in light petroleum was filtered through alumina. Diphenylmethane (3·44 g.) was obtained as colourless needles, m. p. and mixed m. p. 25°. The infrared spectrum was identical with that of an authentic specimen.

4-*Methoxydiphenylmethane from* α-p-*methoxyphenylbenzyl alcohol* (8·0 g.). Isolation as in the previous case and distillation yielded 4-methoxydiphenylmethane (6·7 g.), b. p. 179°/19 mm. (lit., 170°/10 mm.). Demethylation with hydriodic acid gave 4-hydroxydiphenylmethane, needles, m. p. 83—84°. Short and Stewart [9] give m. p. 84°.

4 : 4′-*Dimethoxydiphenylmethane from* 4 : 4′-*dimethoxybenzophenone* (0·54 g.). The crystalline product (0·49 g.) separated from light petroleum as plates, m. p. and mixed m. p. 50—51°.

2 : 4 : 4′-*Trimethoxydiphenylmethane from* 2 : 4 : 4′-*trimethoxybenzophenone* (2·94 g.). The residual oil (2·69 g.) in benzene (5 ml.) was put on alumina and eluted with light petroleum. Evaporation and distillation yielded 2 : 4 : 4′-*trimethoxydiphenylmethane*, b. p. 120—130°/0·07 mm. (Found: C, 74·7; H, 7·1. $C_{16}H_{18}O_3$ requires C, 74·5; H, 7·0%). The infrared spectrum of the liquid showed medium and strong bands at 720, 759, 833, 922, 934, 1034, 1116, 1153, 1172, 1206, 1242, 1290, 1333, 1418, 1439, 1460, 1508, 1595, 1618, 2841, 2941, and 3012 cm.$^{-1}$.

4 : 4′-*Bisdimethylaminodiphenylmethane from Michler's ketone* (2·0 g.). The solid crystallised from ethanol in plates (1·70 g.), m. p. 90·5° (Found: C, 80·2; H, 8·7; N, 11·3. Calc. for

[7] Rainer, Berger, and Nystrom, Amer. Chem. Soc. (Org. Div.) Abs. Papers, Miami, Florida, 1957, p. 51-O.
[8] von Braun, *Ber.*, 1908, **41**, 2113.
[9] Short and Stewart, *J.*, 1929, 553.

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$C_{17}H_{22}N_2$: C, 80·3; H, 8·7; N, 11·0%). Doebner [10] gives m. p. 90°. The compound in ethanol remained colourless on the addition of acetic acid.

Benzanthrene from benzanthrone (4·0 g.). The residual crude benzanthrene was purified on alumina and obtained as pale orange leaflets (3·1 g.), m. p. 83·5—84·5°. Bally and Scholl [11] give m. p. 84°. The picrate separated from alcohol as red needles, m. p. 109—110°. Chatterjee [12] gives m. p. 110—111°.

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[10] Doebner, *Ber.*, 1879, **12**, 810.
[11] Bally and Scholl, *Ber.*, 1911, **44**, 1667.
[12] Chatterjee, *J. Indian Chem. Soc.*, 1943, **20**, 329.

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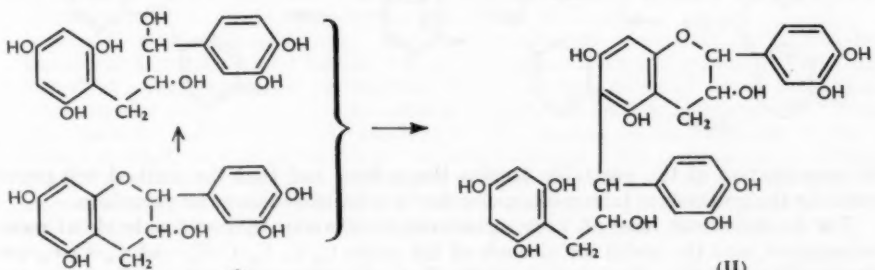
740. *Polymerisation of Flavans. Part I. The Condensation of Methoxybenzyl Alcohols with Phenols.*

By B. R. BROWN, W. CUMMINGS, and G. A. SOMERFIELD.

4-Methoxybenzyl alcohol, *p*-methoxydiphenylmethanol, and 1-*p*-methoxyphenyl-3-phenylpropan-1-ol condense with ethyl acetoacetate, phenol, or resorcinol, and α-*p*-hydroxy- and α-*p*-methoxy-phenylphenethyl alcohol condense with resorcinol in presence of hydrogen chloride in ethanol. Condensation occurs *para* to a phenolic hydroxyl group and yields are in the range 20—70%. The bearing of the condensation on the polymerisation of catechin-like compounds to give tannins is discussed.

COMMERCIAL tannin extracts are complex mixtures of polyphenols, some of which may be polymerised flavans,[1] and some flavans polymerise readily in the presence of mineral acids to give products which have tanning properties.[2] A molecule as complex as catechin (I) may polymerise (*a*) by autoxidation and coupling,[3] (*b*) by the formation of ethers,[4] or (*c*) by a condensation involving the elimination of water,[5] (I) ⟶ (II). The latter mechanism was first postulated by Freudenberg and Maitland [5] over twenty years ago, but has never



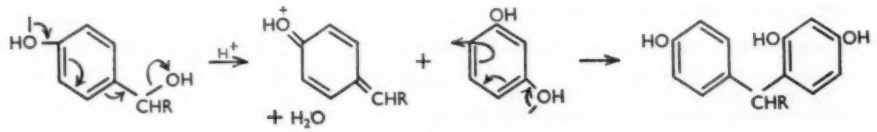
(I) (II)

been tested on simpler compounds, though Freudenberg and Weinges [6] have made a survey of a series of flavans under conditions where all the above polymerisation mechanisms could have operated. To investigate this condensation we have used simple compounds related to the flavans; and, so that mechanism (*c*) would operate to the exclusion of (*a*) and (*b*), methoxy-compounds have been studied. This has the further advantage that experimental difficulties arising from the manipulation of polyphenols

[1] White, Kirby, and Knowles, *J. Soc. Leather Trades' Chemists*, 1952, **36**, 148.
[2] *E.g.*, Etti, *Annalen*, 1877, **186**, 327.
[3] Hathway and Seakins, *Nature*, 1955, **176**, 218.
[4] Cf. Roux, *J. Soc. Leather Trades' Chemists*, 1950, **34**, 122.
[5] Freudenberg and Maitland, *Annalen*, 1934, **510**, 193.
[6] Freudenberg and Weinges, *ibid.*, 1954, **590**, 140.

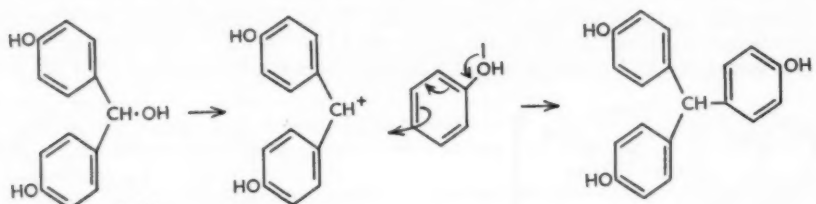
have been avoided, and this has been helped by the methylation of the condensation products. It has thus been possible to use chromatography on alumina for purification.

The activating influence of a *p*-hydroxyl group appears to be responsible for the attack of a benzyl alcohol on a nucleophilic centre in the presence of acid. Though this type of



reaction has not been studied in the exact context presented here, there are sufficient analogies to indicate that such a reaction between simple hydroxy- or methoxy-benzyl alcohols and phenols would be possible. Thus Driver and Sousa [7] investigated the condensation of aromatic aldehydes with phenols and postulated a dihydroxy-intermediate (III) reacting as a carbonium ion. This type of reactivity has been studied in detail by Kenyon *et al.*[8] who have also shown that the simpler molecule *p*-methoxydiphenylmethanol is capable of such alkyl–oxygen fission, and that 2 : 4 : 6-trimethoxydiphenylmethanol condenses with phloroglucinol trimethyl ether in the presence of sulphuric acid. Fosse[9] and Baillon[10] have shown that *p*-methoxydiphenylmethanol readily condenses with malonic acid.

Our aim has been to establish that methoxybenzyl alcohols are capable of reacting as carbonium ions (*e.g.*, with ethyl acetoacetate), and that they are capable of condensing with phenols. A series of benzyl alcohols has been investigated, culminating with alcohols containing the skeleton C_6–C_3–C_6 which is found in the catechin-like molecules that are known to polymerise under acid conditions. It is hoped that the results will be of use in



(III)

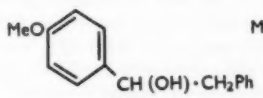
the investigation of the vegetable tannins themselves, and that the method will prove useful for the synthesis of tannin-like molecules by a controlled stepwise procedure.

The condensations have all been carried out in ethanolic hydrogen chloride at room temperature, and the yields for alcohols of the series C_6–C, C_6–C–C_6, and C_6–C_3–C_6 are between 20 and 70%. The alcohols of the C_6–C_2–C_6 series presented a difficulty in the ease with which they yielded stilbenes by dehydration in presence of acids. Thus α-*p*-methoxyphenylphenethyl alcohol (IV) yielded only the stilbene with ethanolic hydrogen chloride and ethyl acetoacetate or phenol. However, with the more reactive resorcinol a condensation product has been isolated. α-*p*-Hydroxyphenylphenethyl alcohol, the only phenolic alcohol studied, yields with resorcinol a condensation product which has been isolated as its tribenzoate.

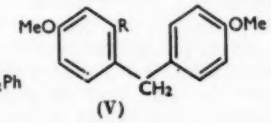
The orientation of the condensation with phenol and resorcinol has been proved in several examples. 4-Methoxybenzyl alcohol and *p*-methoxydiphenylmethanol react at

[7] Driver and Sousa, *J.*, 1954, 985.
[8] Kenyon *et al.*, *J.*, 1942, 605; 1951, 386; 1952, 790, 4964.
[9] Fosse, *Ann. Chim.* (*France*), 1920, **13**, 106.
[10] Baillon, *ibid.*, 1921, **15**, 63.

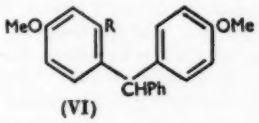
the *para*-position of phenol to yield after methylation the products (V; R = H) and (VI; R = H) whose identities have been established by comparison with specimens synthesised by known methods. Condensation of the same two alcohols with resorcinol occurs in the 4-position to yield after methylation the ethers (V; R = OMe) and (VI;



(IV)



(V)



(VI)

R = OMe). 2 : 4 : 4′-Trimethoxydiphenylmethane (V; R = OMe) was identified by comparison with a specimen synthesised by the hydrogenolysis of 2 : 4 : 4′-trimethoxybenzophenone with aluminium chloride and lithium aluminium hydride,[11] and 2 : 4 : 4′-trimethoxytriphenylmethane (VI; R = OMe) was obtained from the same ketone by a Grignard synthesis followed by reduction of the alcohol. Thus in these examples the condensation has taken place preferentially in the *para*-position to a hydroxyl group, and this orientation has been assumed in the other products.

Experimental

The light petroleum was of b. p. 40—60° unless otherwise stated.

4-*Methoxyphenethyl Methyl Ketone*.—Dry hydrogen chloride was passed through a solution of 4-methoxybenzyl alcohol (1·0 g.) in ethyl acetoacetate (10 ml.) for 15 min., during which the temperature rose to 50—60°. After 30 min. at room temperature, the mixture was heated at 90° for 10 min., and added to a solution of potassium hydroxide (10 g.) in ethanol (80 ml.). This mixture was boiled under reflux for 1½ hr., then poured into water (400 ml), and the ketone extracted in ether. Evaporation yielded the crude ketone (0·45 g.) as a pale brown oil. The semicarbazone separated from methanol as colourless needles, m. p. 168—169°. Strauss and Grindel [12] record m. p. 169—170°. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as orange needles, m. p. 141—142° (Found, in material dried at 80°/10 mm. for 4 hr.: C, 57·2; H, 4·8; N, 15·3. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·0; N, 15·6%).

4 : 4′-*Dimethoxydiphenylmethane*.—Dry hydrogen chloride was passed for 10 min. into a solution of 4-methoxybenzyl alcohol (1·0 g.) and phenol (1·0 g.) in ethanol (10 ml.). After 7 days at room temperature the mixture was poured into excess of water, the orange oil extracted with ether, and the ethereal solution washed with water to remove phenol. Evaporation yielded a red oil which was dissolved in 10% aqueous sodium hydroxide (40 ml.) and treated gradually with an excess (5·0 ml.) of methyl sulphate. The methylation was completed at 100° (30 min.) and the product extracted from the cold mixture with ether. The oil obtained on evaporation was dissolved in benzene (3·0 ml.) and put on a column of alumina. Elution with light petroleum (350 ml.) and evaporation yielded colourless plates (0·47 g.), m. p. and mixed m. p. 51—52°.

2 : 4 : 4′-*Trimethoxydiphenylmethane*.—An experiment identical with that recorded above, but with resorcinol (1·0 g.) in place of phenol, yielded a pale yellow oil (0·51 g.) on evaporation of the light petroleum eluate. Distillation at 120—130°/0·02 mm. gave 2 : 4 : 4′-trimethoxydiphenylmethane as a colourless viscous oil (Found: C, 74·5; H, 7·3. Calc. for $C_{16}H_{18}O_3$: C, 74·5; H, 7·0%). A comparison of b. p.s and infrared spectra proved the compound to be identical with a sample produced by hydrogenolysis of 2 : 4 : 4′-trimethoxybenzophenone.[11]

α-4-*Methoxyphenylphenethyl Methyl Ketone*.—Dry hydrogen chloride was passed for 5 min. through a solution of *p*-methoxydiphenylmethanol (0·50 g.) in ethyl acetoacetate (5·0 ml.), and the solution was kept at room temperature for 30 min. and then heated for 10 min. at 90°. The solution obtained by the addition of potassium hydroxide (5·0 g.) and ethanol (40 ml.) was boiled for 1 hr., then poured into excess of water. The precipitated yellow solid was crystallised twice from aqueous ethanol to yield the *ketone* (0·30 g.) as colourless prisms, m. p. 60—61°

[11] Brown and White, preceding paper.
[12] Strauss and Grindel, *Annalen*, 1924, **439**, 303.

(Found: C, 80·7; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The 2 : 4-*dinitrophenylhydrazone* separated from methanol as yellow needles, m. p. 136—137° (Found: C, 63·55; H, 4·95. $C_{23}H_{22}O_5N_4$ requires C, 63·6; H, 5·05%).

4 : 4′-*Dimethoxytriphenylmethane*.—A solution of *p*-methoxydiphenylmethanol (1·0 g.) and phenol (1·0 g.) in ethanol (10 ml.) was treated with hydrogen chloride for 10 min. and kept at room temperature for 7 days. The mixture was poured into water (80 ml.) previously saturated with nitrogen, and the resulting white precipitate was extracted with ether, the ethereal layer washed with water to remove phenol, and the product removed by extraction with 10% aqueous sodium hydroxide (30 ml.). The alkaline solution was treated gradually with methyl sulphate (2·0 g.), methylation completed at 100° (20 min.), and the product extracted from the cold mixture with ether. Evaporation yielded a pale brown oil which was dissolved in benzene (2·0 ml.) and put on a column of alumina. Elution with light petroleum and evaporation yielded colourless crystals (0·47 g.). Recrystallisation from light petroleum gave 4 : 4′-dimethoxytriphenylmethane as colourless plates, m. p. and mixed m. p. 100·5—101·5° (Found: C, 83·05; H, 6·55. Calc. for $C_{21}H_{20}O_2$: C, 82·9; H, 6·6%).

2 : 4 : 4′-*Trimethoxytriphenylmethane*.—(a) *By condensation*. *p*-Methoxydiphenylmethanol (1·0 g.) and resorcinol (1·0 g.) in ethanol (10 ml.) was treated with hydrogen chloride for 10 min. and kept at room temperature for 2 days. The solution was poured into water (70 ml.; previously saturated with nitrogen) and the product isolated and methylated as previously described. The product in benzene (5·0 ml.) was put on a column of alumina and eluted with light petroleum (400 ml.) to yield a colourless oil (0·5 g.), which separated from light petroleum or alcohol as colourless crystals, m. p. 99—100° (Found: C, 79·6, 79·5; H, 6·6, 6·6. $C_{22}H_{22}O_3$ requires C, 79·05; H, 6·55%). Passage through a second column of alumina and crystallisation from light petroleum (b. p. 40—45°) yielded 2 : 4 : 4′-*trimethoxytriphenylmethane* as needles, m. p. 108—109° (Found: C, 78·9; H, 6·6%). The m. p. was unchanged on admixture of the compound with a specimen synthesised as described below.

(b) *By synthesis*. (i) 2 : 4 : 4′-Trimethoxytriphenylmethanol. The Grignard solution from bromobenzene (4·0 g.), magnesium (0·6 g.), and ether (15 ml.) was added at 0° to 2 : 4 : 4′-trimethoxybenzophenone (4·7 g.) in ether (150 ml.), and the reaction completed at 35° for 30 min. The usual method of isolation gave a red oil which was put on a column of alumina and eluted with 5 : 1 light petroleum–benzene to yield an oil (2·3 g.) which from light petroleum (b. p. 60—80°) gave 2 : 4 : 4′-*trimethoxytriphenylmethanol* as colourless needles, m. p. 109—110° (Found: C, 75·55; H, 6·25. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%). Elution of the column with 1 : 1 light petroleum–benzene gave unchanged 2 : 4 : 4′-trimethoxybenzophenone (2·2 g.), m. p. 69—71°.

(ii) 2 : 4 : 4′-Trimethoxytriphenylmethane. The above alcohol (0·4 g.) in ethanol (35 ml.) and concentrated hydrochloric acid (2·5 ml.) was boiled until the purple colour was discharged. Addition of water caused the triphenylmethane (0·2 g.) to separate, and recrystallisation from light petroleum gave colourless needles, m. p. 108—109° (Found: C, 79·4; H, 6·7%).

α-p-*Hydroxyphenylphenethyl Alcohol*.—To the Grignard solution from benzyl chloride (16·0 g.), magnesium (3·2 g.), and ether (70 ml.) was added a solution of *p*-hydroxybenzaldehyde (6·1 g.) in ether (125 ml.). The mixture was boiled under reflux for 20 min. and decomposed at 0° with dilute hydrochloric acid. The ether layer was washed with sodium hydrogen carbonate solution, sodium hydrogen sulphite solution, and finally water. Evaporation yielded the solid *alcohol* which separated from aqueous methanol as needles (2·2 g.), m. p. 157—158° (Found: C, 78·4; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·55%). The *benzoate* separated from aqueous ethanol as hydrated needles, m. p. 87—88°, but from light petroleum (b. p. 60—80°) as colourless needles, m. p. 100—101° (Found: C, 79·8; H, 5·75. $C_{21}H_{18}O_3$ requires C, 79·3; H, 5·65%).

4-*Hydroxystilbene*.—A solution of the above alcohol in benzene was boiled for 5 min. in presence of a trace of hydrogen chloride. The cold solution deposited colourless plates which on recrystallisation from aqueous methanol had m. p. 187° (Found: C, 85·95; H, 6·2. Calc. for $C_{14}H_{12}O$: C, 85·7; H, 6·1%). Guss, Williams, and Jules [13] give m. p. 186—187·5°. The *benzoate* separated from acetone–ethanol as needles, m. p. 196° (Found: C, 83·6; H, 5·3. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·35%).

1-p-*Benzoyloxyphenyl*-1-(2 : 4-*dibenzoyloxyphenyl*)-2-*phenylethane*.—Dry hydrogen chloride was passed for 5 min. into a solution of α-*p*-hydroxyphenylphenethyl alcohol (0·40 g.) and resorcinol (0·25 g.) in ethanol (10 ml.). The solution was warmed to 70°, kept at room temperature for 3 days, and poured into water (60 ml.) to yield a sticky solid which was isolated by

[13] Guss, Williams, and Jules, *J. Amer. Chem. Soc.*, 1951, **73**, 1257.

means of ether, dissolved in aqueous sodium hydroxide, and shaken with excess of benzoyl chloride. The sticky solid which separated became a white solid on being boiled with ethanol, and two crystallisations from acetone–ethanol gave the *tribenzoate* (0·60 g.) as needles, m. p. 213—214·5° (Found: C, 79·95; H, 4·9. $C_{41}H_{30}O_6$ requires C, 79·6; H, 4·85%).

1-(2 : 4-*Dihydroxyphenyl*)-1-p-*methoxyphenyl*-2-*phenylethane*.—A solution of α-*p*-methoxyphenylphenethyl alcohol (0·7 g.) and resorcinol (0·4 g.) in ethanol (10 ml.) was treated with dry hydrogen chloride for 10 min. After a day at room temperature, the solution was poured into water, the resulting precipitate extracted with ether, and the ethereal layer washed with water to remove resorcinol. Evaporation of the ether yielded a pale orange, sticky solid which after several crystallisations from benzene gave the *ethane* (0·20 g.) as colourless prisms, m. p. 178—179° (Found, in material dried at 120°/0·1 mm. for 6 hr.: C, 78·7; H, 6·3. $C_{21}H_{20}O_2$ requires C, 78·8; H, 6·3%).

4-p-*Methoxyphenyl*-6-*phenylhexan*-2-*one*.—A solution of 1-*p*-methoxyphenyl-3-phenylpropan-1-ol (1·0 g.) in ethyl acetoacetate (10 ml.) was treated with dry hydrogen chloride for 30 min. After 15 min. at 100° the mixture was added to a solution of potassium hydroxide (10 g.) in ethanol (80 ml.) and boiled under reflux for 2 hr. The cold mixture was poured into excess of dilute hydrochloric acid, and the ketone extracted with ether. Evaporation yielded a brown oil which was dissolved in 4 : 1 light petroleum–benzene and put on a column of alumina. Elution with the same solvent mixture (350 ml.) and evaporation gave colourless crystals which were crystallised from light petroleum to yield 4-p-*methoxyphenyl*-6-*phenylhexan*-2-*one* (0·15 g.) as needles, m. p. 53—54° (Found: C, 80·8; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·6%). The infrared spectrum showed a carbonyl band at 1709 cm.$^{-1}$. The dinitrophenylhydrazone was an oil.

1 : 1-*Di*-p-*methoxyphenyl*-3-*phenylpropane*.—A solution of 1-*p*-methoxyphenyl-3-phenylpropan-1-ol (1·0 g.) and phenol (1·0 g.) in ethanol (10 ml.) was treated with hydrogen chloride for 10 min. and kept at room temperature for 7 days. Isolation and methylation as usual yielded a brown oil which was dissolved in benzene (3·0 ml.), put on alumina, and eluted with light petroleum (500 ml.). Evaporation gave 1 : 1-*di*-p-*methoxyphenyl*-3-*phenylpropane* (0·89 g.) which separated from light petroleum as needles, m. p. 43—44·5° (Found: C, 83·5; H, 7·5. $C_{23}H_{24}O_2$ requires C, 83·1; H, 7·4%).

1-(2 : 4-*Dimethoxyphenyl*)-1-p-*methoxyphenyl*-3-*phenylpropane*.—An experiment identical with that described above but with resorcinol in place of phenol yielded, after methylation and chromatography, a pale yellow oil (0·175 g.). Distillation at 150—155°/0·01 mm. gave the *propane* as a colourless oil (Found: C, 80·0; H, 7·2. $C_{24}H_{26}O_3$ requires C, 79·6; H, 7·2%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, April 23rd*, 1957.]

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741. *Complex Fluorides. Part IX.* The Lattice Constants and Infrared Spectra of the Fluorosulphates.*

By D. W. A. SHARP.

The valencies of the fluorosulphate ion SO_3F^- are directed from the central sulphur atom towards the corners of a tetrahedron. The potassium, ammonium, and rubidium salts are isomorphous with the perchlorates and are ionic, but in other salts there is evidence for distortion of the anion by partial covalent-bond formation. The infrared spectra agree closely with the published Raman spectrum for the fluorosulphate ion. Assignments are made for infrared peaks observed and the differences between the infrared and Raman spectra are discussed. The ammonium salt shows strong evidence for hydrogen bonding.

KETELAAR and WEGERIF [1] showed that the structures of salts AMX_4^{n-} having tetrahedral anions are all closely related. It was not considered necessary that the ligands, X, should all be the same, the fluorochromates $MCrO_3F$ and the osmiamates $MOsO_3N$ forming part of the series. The series is now extended to include the fluorosulphates.

* Part VIII, *J.*, 1957, 674.

[1] Ketelaar and Wegerif, *Rec. Trav. chim.*, 1938, **57**, 1269.

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Lange [2] showed that, from gross morphology, potassium fluorosulphate appears to be isomorphous with potassium perchlorate and Seifert,[3] from *X*-ray crystallography, that cæsium fluorosulphate has the scheelite structure and is probably isomorphous with cæsium fluorochromate. Since potassium fluorochromate also has a pseudo-scheelite structure,[1] potassium and rubidium fluorosulphates should have either the scheelite structure of the fluorochromates, or the barium sulphate structure of the perchlorates.

Potassium, rubidium, and ammonium fluorosulphates are orthorhombic at room temperature, probably having the space group *Pnma*; they are isomorphous with the corresponding perchlorates. Cell sides were found to be as follows: KSO_3F: $a_0 = 8{\cdot}57 \pm 0{\cdot}03$; $b_0 = 5{\cdot}93 \pm 0{\cdot}05$; $c_0 = 7{\cdot}36 \pm 0{\cdot}03$ Å; $RbSO_3F$: $a_0 = 9{\cdot}21 \pm 0{\cdot}03$; $b_0 = 5{\cdot}80 \pm 0{\cdot}05$; $c_0 = 7{\cdot}67 \pm 0{\cdot}03$ Å; NH_4SO_3F: $a_0 = 8{\cdot}79 \pm 0{\cdot}03$; $b_0 = 6{\cdot}07 \pm 0{\cdot}05$; $c_0 = 7{\cdot}32 \pm 0{\cdot}03$ Å, and the unit cell volumes were 375, 410, and 386 Å^3 for potassium, rubidium, and ammonium fluorosulphates respectively. The unit cells are not completely regular as regards axial ratios, $a : b : c$ being 1·445 : 1 : 1·242 for KSO_3F, 1·585 : 1 : 1·320 for $RbSO_3F$, and 1·449 : 1 : 1·208 for NH_4SO_3F, but this lack of regularity probably only reflects the slightly differing cation sizes in a fairly complex lattice and the presence of hydrogen bonding in the ammonium salt.

The unit-cell volume of the ammonium salt lies closer to that of the potassium salt than of the rubidium salt. For salts of complex fluoro-acids the ammonium salt generally has a rather larger unit-cell volume than the rubidium salt, the complex chloro- and bromo-salts having the reverse relationship.[4] The small unit-cell volume in the present salt is possibly due to hydrogen-bond formation, and this would also account for the non-regularity in axial ratios. Its existence is clearly shown in the infrared spectrum of ammonium fluorosulphate.

Sodium fluorosulphate gives a powder pattern similar to that of anhydrous sodium perchlorate, which has the anhydrite structure,[5] but the pattern could not be indexed and the two salts are probably not isomorphous. The greater polarizing power of the sodium ion would make it the most likely of all the alkali metals examined to distort the fluorosulphate ion. Silver fluorosulphate gives a very different powder pattern from potassium fluorosulphate and there is probably some covalent-bond formation between the silver and the fluorosulphate group. Such covalent-bond formation appears quite general amongst silver salts of oxyanions.[6] The distortion of the fluorosulphate ion inferred from the *X*-ray data for these two salts is confirmed by the infrared spectra; such distortion will lower the symmetry of the anion and give rise to the possibility of many more infrared absorption peaks.

Thus, crystallographic evidence shows that the fluorosulphates are isomorphous with the perchlorates, having tetrahedral symmetry about the central sulphur atom. Such an ion will have the symmetry group C_{3v}, having six fundamental modes of vibration, all of which will be both infrared- and Raman-active. An assignment had already been made to all the infrared bands observed and the assignments were completely confirmed by Siebert's Raman spectra.[7] Complete values for the observed infrared and Raman frequencies are given in the Table, together with the assignments for the various bands. Within the limits of experimental error, the values found for most of the fundamentals are in good agreement when the results of infrared and Raman spectroscopy are compared. The only major disagreement is in the value for the S–F stretching frequency, ν_2. The value for the symmetrical S–F stretching in sulphur hexafluoride [8] is 775 cm.$^{-1}$ and Siebert records 786 cm.$^{-1}$ for the corresponding Raman frequency for an aqueous solution of

[1] Lange, *Ber.*, 1929, **62**, 786.
[2] Seifert, *Z. Krist.*, 1942, **104**, 385.
[3] Cox and Sharpe, *J.*, 1954, 1798.
[4] Zachariasen, *Z. Krist.*, 1930, **73**, 141.
[5] Sharp and Sharpe, unpublished results.
[6] Siebert, *Z. anorg. Chem.*, 1957, **289**, 15.
[7] Eucken and Ahrens, *Z. phys. Chem.*, 1934, *B*, **26**, 297; Yost, Steffens, and Gross, *J. Chem. Phys.*, 1934, **2**, 311.

sodium fluorosulphate.[7] Siebert comments that this value is surprisingly high as it would be expected that the high "ionic-character" of the bond $O_2S(O^-)-F \rightleftharpoons O_2S(:O) + F^-$ would lower this frequency as in the analogous case of boron trifluoride and the fluoroborate ion [9] (symmetrical B–F stretching frequencies 888 and 771 cm.$^{-1}$ respectively). For both the fluoroborate and the fluorosulphate ions, removal of the fluoride ion leaves

Infrared and Raman spectra of the fluorosulphates.

$NaSO_3F$	KSO_3F	$RbSO_3F$	$CsSO_3F$	NH_4SO_3F	$AgSO_3F$	$Ph_3C{\cdot}SO_3F$ [a]	$NaSO_3F$ [b]	Assignment	Calc.	Notes
*	—	*	*	*	*	*	409	ν_6 (E_1)	390	(1)
*	565 m	*	*	*	*	*	566	ν_3 (A_1)	—	(2)
	583 s						592	ν_5 (E)	—	(3)
740 m	732 s	729 s	728 s	737 s	767 s	710 m	786	ν_2 (A_1)	—	(4)
785 s	—	—	—	—	785 s	—	—	—	—	
—	970 w	973 w	971 w	970 w	975 w	—	—	$\nu_6 + \nu_3$	955	
								$\nu_6 + \nu_5$	973	
1095 s	1073 s	1072 s	1071 s	1072 s	1057 s	1070 s	1082	ν_1 (A_1)	—	(5)
1275 s	1277 s	1274 s	1258 s	1270 s	1235 s	—	—	$\nu_2 + \nu_5$	1315	
1295 s	1299 s	1294 s	1300 s	1304 s	1282 s	1289 s	1287	ν_4 (E)	—	(6)
—	1656 w	1661 w	1662 w	—	1631 s	1643 w	—	$\nu_1 + \nu_5$	1656	
2370 w	2347 w	2342 w	2353 w	—	2273 w	2320 w	—	$\nu_1 + \nu_4$	2372	

[a] Sharp and Sheppard, ref. 11. [b] Raman spectrum; Siebert, ref. 7. * Not examined below 650 cm.$^{-1}$.

Notes.—(1) Rock. (2) Symmetrical SO_3 deformation. (3) Asymmetrical SO_3 deformation. (4) S–F stretching. (5) Symmetrical S–O stretching. (6) Asymmetrical S–O stretching.

a stable, known entity. We have concluded that the difference in S–F stretching frequencies in the solid state and in aqueous solution is due, in the latter case, to some form of hydrogen bonding between the water molecules and the oxygen atoms of the fluorosulphate ion. This would reduce the possible "ionic character" of the S–F bond and its frequency would approach that found in sulphur hexafluoride. Similar distortion is most likely to occur in the solid state with cations of high polarizing power and it is significant that sodium fluorosulphate gives a strong infrared band at 785 cm.$^{-1}$. A similar band is found in silver fluorosulphate, but here the symmetry of the anion has been destroyed and other additional bands occur. Siebert [10] has come to a very similar conclusion on the value of the S–F stretching frequency, and has found that there is a similar result for all the ions XSO_3^- when the values of the S–X frequencies are compared in the solid and in solution. Extra infrared bands are a good criterion for anion–cation interaction and triphenylmethyl fluorosulphate is completely ionic in character.[11]

The assignments of the other infrared bands follow simply from the relations between the observed frequencies of the sulphate ion (symmetry group T_d), the fluorosulphate ion (symmetry group C_{3v}), and sulphuryl fluoride (symmetry group C_{2v}). The infrared absorption pattern of the fluorosulphate ion is very similar to that of the isoelectronic perchloryl fluoride.[12] For the fairly strong band at 1277 cm.$^{-1}$ the combination frequency $\nu_2 + \nu_5$ was preferred. This was considered more probable than the alternative of $\nu_2 + \nu_3$, as Fermi resonance will occur between the fundamental ν_4 and the combination frequency to give enhanced intensity to the latter. By comparison with the spectrum of perchloryl fluoride the absorption band corresponding to the vibration ν_6 should lie below 400 cm.$^{-1}$, that is, out of the range of the potassium bromide prism. If the weak absorption peak at 970 cm.$^{-1}$ corresponds to either of the combinations $\nu_3 + \nu_6$ or $\nu_5 + \nu_6$, this would lead to a value of about 390 cm.$^{-1}$ for the vibration ν_6.

The infrared frequencies of the ammonium ion in ammonium fluorosulphate occur at 1410, 1448, 3040, and 3125 cm.$^{-1}$. The position of the N–H vibration at about 1400 cm.$^{-1}$ has been used as diagnostic of the presence of hydrogen bonding [13] and the splitting of this,

[9] Siebert, *Z. anorg. Chem.*, 1953, **274**, 34.
[10] *Idem*, personal communication.
[11] Sharp and Sheppard, *J.*, 1957, 674.
[12] Lide and Mann, *J. Chem. Phys.*, 1956, **25**, 1128.
[13] Bovey, *ibid.*, 1950, **18**, 1684.

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and of the 3100 cm.$^{-1}$ band, in the spectrum of this salt shows the presence of this form of linkage. However, the hydrogen bonding does not seem sufficiently strong to affect the fluorosulphate ion frequencies, although the displacement of the 1400 cm.$^{-1}$ band to 1448 cm.$^{-1}$ is greater than that hitherto recorded for any ammonium salt except ammonium fluoride. The splitting of this band is similar to that observed by Wagner and Hornig [14] for the low-temperature form of ammonium chloride.

Experimental

The fluorosulphates were prepared by Woolf's method [15] and analysed by evaporation with concentrated hydrochloric acid and estimation as barium sulphate. Sodium fluorosulphate was prepared from bromine trifluoride and sodium persulphate (Found: SO_3F^-, 81·1. Calc. for $NaSO_3F$: SO_3F^-, 82·1%), potassium fluorosulphate from bromine trifluoride and potassium persulphate (Found: SO_3F^-, 71·4. Calc. for KSO_3F: SO_3F^-, 71·6%), and rubidium fluorosulphate from bromine trifluoride and an equimolecular mixture of rubidium chloride and nitrosonium pyrosulphate (Found: equiv., 190; SO_3F^-, 52·8. Calc. for $RbSO_3F$: equiv., 185; SO_3F^-, 53·6%). Cæsium fluorosulphate was prepared as an equimolecular mixture with cæsium fluoride from bromine trifluoride and cæsium sulphate, the products being heated to 250° to destroy cæsium bromofluoride. It was identified by means of its *X*-ray powder photograph.[3] Ammonium fluorosulphate was prepared by heating ammonium pyrosulphate with ammonium fluoride followed by extraction of the required salt with ammoniacal methyl alcohol [16] (Found: N, 12·2. Calc. for NH_4SO_3F: N, 12·0%), and silver fluorosulphate from bromine trifluoride and an equimolecular mixture of silver chloride and nitrosonium pyrosulphate (Found: Ag, 52·2. Calc. for $AgSO_3F$: Ag, 52·1%).

X-Ray powder photographs were taken with Cu-$K\alpha$ radiation. The samples were filled into Pyrex capillaries, the " dry-box " technique being used for $NaSO_3F$ and $AgSO_3F$, and the capillaries were sealed with warm picein wax. *X*-Ray powder photographs were indexed by analogy with the known structure of potassium perchlorate.[17]

Infrared spectra were measured in Nujol and hexachlorobutadiene mulls on a Perkin-Elmer Model 21 spectrometer with rock-salt or potassium bromide optics. Where necessary, mulls were prepared in the " dry-box."

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University Chemical Laboratory, Cambridge. [*Received, May 6th*, 1957.]

[14] Wagner and Hornig, *ibid.*, 1950, **18**, 296.
[15] Woolf, *J.*, 1950, 1053.
[16] Mellor, " A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., London, 1930, p. 685.
[17] Gottfried and Schusterius, *Z. Krist.*, 1932, **84**, 65.

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742. *The Sex-attractant of the Silkworm Moth* (Bombyx mori).

By El S. Amin.

The sex-attractant of the female silkworm moth has been identified as dimethylamine. It has been isolated from the sacculi lateralis as *p*-*p*'-nitrophenylazobenzoyl derivative which on hydrolysis gives an attractant solution. A chromatographic procedure is described for separation of mixtures of simple primary and secondary amines as *p*-*p*'-nitrophenylazobenzoyl derivatives.

Female silkworm moths (*Bombyx mori*), soon after hatching, develop two sacks (sacculi lateralis) at the tip of the abdomen.[1] These sacks contain a material which acts as a powerful attractant for male moths.[2] After early work on different moths had been

[1] Freiling, *Wissensch. Zool.*, 1909, 92.
[2] Fabre, " Social life in the insect world," translated by B. Miall, Pelican, London, 1943; Flaschenträger and Amin, *Nature*, 1950, **165**, 394; *Angew. Chem.*, 1949, **61**, 252; Götz, *Experientia*, 1951, **7**, 406.

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ineffective,[3] Butenandt [4] hydrolysed the material in the sacks from 313,000 silkworm moths, converted the non-acidic portion into *p*-*p*′-nitrophenylazobenzoyl derivatives and by counter-current fractionation and chromatography obtained material, m. p. 58—68°, giving on hydrolysis a product which was active as a sex-attractant in amounts as low as 10^{-11} g. But he did not identify this active product.

The present author extracted the sacculi lateralis of 3428 female moths with light petroleum, without prior hydrolysis, warmed the resultant solution with *p*-*p*′-nitrophenylazobenzoyl chloride, pyridine, and benzene, concentrated the solution, removed the pyridine and free acid, and then by chromatography, partition chromatography, and crystallisation, obtained 13·5 mg. of a pure derivative, m. p. 178°, which on hydrolysis gave a solution which was highly attractant to male moths.

The simple alkyl *p*-*p*′-nitrophenylazobenzoates had been prepared by Amin and Hecker, who also devised a chromatographic technique for their separation.[5,6] However, none of these esters resembled the materials isolated from silkworm moths. This work has now been extended to *p*-*p*′-nitrophenylazobenzoyl derivatives of ten simple primary and secondary amines. The derivative of dimethylamine is identical with the compound, m. p. 178°.

Dimethylamine is therefore the sex-attractant of the female silkworm.

In the Experimental section is described also a partition-chromatographic method of separating the amines by means of their *p*-*p*′-nitrophenylazobenzoyl derivatives on kieselguhr impregnated with dimethyloxosilane.

Experimental

Evaporations were under reduced pressure at 50°. M. p.s were determined on the Kofler microscope stage.

Substituted p-p′-*Nitrophenylazobenzamides*.—(a) *Preparation*. The amine (0·5 millimole) and *p*-*p*′-nitrophenylazobenzoyl chloride [4] (0·725 millimole) were heated in 1 : 1 pyridine–benzene (14 ml.) at 50° for 6 hr. The mixture was then treated with water and extracted with benzene (50 ml.). The extract was washed with 20% sulphuric acid, filtered, washed successively with water, sodium carbonate solution, and water, concentrated to *ca.* 10 ml., and filtered through a column of alumina. The main, lower, red band was eluted with benzene, and the product recrystallised (forming needles) from ethanol, acetone, nitromethane, nonane, decane, or dimethylformamide. The p-p′-*nitrophenylazobenzoyl derivatives* recorded in the Table were thus obtained in 94—98% yield.

(b) *Hydrolysis*. The amine in benzene or *cyclo*hexane was warmed with 1 equiv. of potassium hydroxide in 2-methoxyethanol for 2 hr. at 50°. Potassium *p*-*p*′-nitrophenylazobenzoate was then filtered off, leaving the amine in solution.

(c) *Chromatography*. Kieselguhr (0·5 kg.) was dried at 110° and placed in a desiccator over dichlorodimethylsilane for 3 days, being occasionally shaken. The kieselguhr was then treated with water (1·5 l.), and the floating material was collected, washed with methanol to neutrality, and dried at 110°.

A 20 : 1 (v/v) mixture of 50% (v/v) aqueous acetone and chloroform was shaken and the two layers were separated. A Pyrex chromatography tube (*ca.* 40 cm. long and 2·0 cm. in diameter) was half-filled with the acetone layer, then a 1 : 1 (w/w) mixture of the chloroform layer and the treated kieselguhr was added, 15 g. at a time, with slight suction, air being removed by manipulation of a plunger. When the column had drained, a solution of the acylamine (⩾15 mg.) in the acetone layer was added, and the chromatogram was developed with further quantities of the acetone layer. The colour in successive fractions was determined electrophotometrically.

Alternatively, 45% of 65% (v/v) aqueous dimethylformamide was shaken with carbon

[3] Amin, Thesis, Alexandria, 1949, 1952; Haller, Acree, and Potts, *J. Amer. Chem. Soc.*, 1944, **66**, 1659; Acree, *J. Econ. Entomol.*, 1953, **46**, 313.
[4] Butenandt, *Naturwiss. Rundschau*, 1955, **8**, 457.
[5] Amin and Hecker, *Chem. Ber.*, 1956, **89**, 695.
[6] Hecker, *Chem. Ber.*, 1955, **88**, 1666.

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tetrachloride, the carbon tetrachloride layer being mixed with the kieselguhr, and the aqueous dimethylformamide layer used as solvent and eluant.

Amine	Colour	Solvent	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
NH_2Me	Red	$MeNO_2$	233°	—	—	—	—	—	—	—
NH_2Et	Red	EtOH	220	60·2	4·8	19·1	$C_{15}H_{14}O_3N_4$	60·4	4·7	18·8
NH_2Pr^a	Orange	$MeNO_2$	187	61·2	5·4	17·7	$C_{16}H_{16}O_3N_4$	61·5	5·2	17·9
NH_2Bu^a	,,	$COMe_2$	197	62·6	5·55	—	$C_{17}H_{18}O_3N_4$	62·6	5·6	—
*cyclo*Hexylamine	,,	,,	248	64·3	5·9	15·4	$C_{19}H_{20}O_3N_4$	64·75	5·7	15·9
*iso*Pentylamine	,,	,,	168	—	—	—	—	—	—	—
$CH_2Ph{\cdot}NH_2$	Red	EtOH	236	66·8	4·5	—	$C_{20}H_{16}O_3N_4$	66·7	4·5	—
$NHMe_2$	Orange-red	C_6H_{10}	178	60·3	4·6	19·1	$C_{15}H_{14}O_3N_4$	60·4	4·7	18·8
$NHEt_2$	Orange	$C_{10}H_{22}$	162	62·1	5·3	17·0	$C_{17}H_{18}O_3N_4$	62·6	5·5	17·2
$NHBu_2^a$	,,	EtOH	130	—	—	—	—	—	—	—

Suitable eluant fractions were combined and evaporated, the residue was extracted with benzene, the benzene extract in turn evaporated, and this residue crystallised from ethanol.

The following results are typical.

(i) A mixture of *p*-*p*′-nitrophenylazobenzoyl derivatives (1 mg. each) of ethylamine, propylamine, and butylamine was chromatographed as above, but on a 10 × 2 cm. column, with the aqueous-acetone–chloroform system. Eluant fractions taken were: nos. 1—21, 2 ml.; nos. 22—31, 4 ml.; nos. 32—42, 6 ml. each. Fractions 1—15 yielded 0·8 mg. of ethylamide; fractions 16—31 yielded 0·6 mg. of propylamide; fractions 32—42 yielded 0·6 mg. of butylamide. These amides were identified by m. p.s and mixed m. p.s.

(ii) When the above mixture was chromatographed with the 45% aqueous-dimethylformamide–carbon tetrachloride system, the photometric readings showed a trace of overlap between the ethylamide and propylamide but a gap of 10 fractions between the propylamide and butylamide.

(iii) Use of the 65% aqueous-dimethylformamide–carbon tetrachloride system separated the dimethylamide from the diethylamide with a gap of two fractions.

Isolation of the Attractant.—Pupæ of 5000 silkworms were removed from the cocoons and the females separated. After hatching, the tips of the abdomen of 3428 female moths were cut off and placed at once under light petroleum (b. p. 50—60°) (500 ml.). The collected tips were crushed with sand and re-extracted with light petroleum (2 l.). The combined petroleum extracts were dried (Na_2SO_4), mixed with dry benzene (1 l.), *p*-*p*′-nitrophenylazobenzoyl chloride (0·5 g.), and pyridine (10 ml.), and heated under reflux at 50° until the solution was no longer attractant to male moths (6 hr.). The solution was concentrated to 250 ml., washed with 20% sulphuric acid, filtered, washed in turn with water, sodium carbonate solution, and water, and placed on an alumina column. Of the two coloured bands produced, the lower, red band was eluted with benzene, giving 18·54 mg. of material which on hydrolysis gave a solution attractant to male moths. The upper band, on elution with benzene, gave a non-attractant orange oil (76·9 mg.).

The attractant material (17·5 mg.) was subjected to partition chromatography on treated kieselguhr, as described above, but the decane–nitromethane system was used, giving two bands. Elution of the main, lower band with the nitromethane layer and recrystallisation of recovered material from decane gave orange-red needles (13·5 mg.), m. p. 178° alone or mixed with *NN*-dimethyl-*p*-*p*′-nitrophenylbenzamide (Found: C, 60·7; H, 4·6; N, 18·9. $C_{15}H_{14}O_3N_4$ requires C, 60·4; H, 4·7; N, 18·8%). Partition chromatography of this product with the 65% aqueous-dimethylformamide–carbon tetrachloride system gave no indication of heterogeneity.

The upper, pale orange band afforded cholesteryl *p*-*p*′-nitrophenylazobenzoate (1 mg.), m. p. 180°, which was not attractant after hydroysis.

Faculty of Science,
Alexandria University, Egypt.

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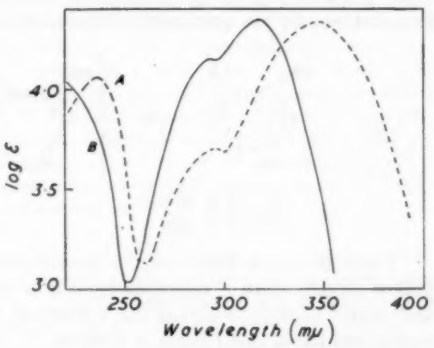
743. *The Isomeric Pyruvamide Phenylhydrazones.*

By R. A. Abramovitch and Ian D. Spenser.

syn- and *anti*-Structures are assigned to the pairs of pyruvamide phenylhydrazones and methyl pyruvate phenylhydrazones on the basis of infrared spectra, hydrogen-bonding occurring in the *syn*-forms.

Pyruvamide phenylhydrazone was first reported by Gastaldi [1] who obtained it as colourless plates, m. p. 144°, by reduction of *N*-hydroxypyruvamide phenylhydrazone with sodium amalgam. The product prepared from pyruvamide and phenylhydrazine in dilute hydrochloric acid [2] was similar to Gastaldi's, whereas that prepared in dilute alcohol [3] was obtained as yellow needles, m. p. 118—119°.

We have now found that the yellow modification is also formed in dilute acetic acid and may be converted into the colourless form by recrystallisation from water containing a trace of alkali, or in the cold by treatment with dilute mineral acid or with chloroform. It has not been possible to effect the reverse transformation; when an aqueous or ethanolic solution of the colourless modification was treated with ammonia or sulphur dioxide [4] a yellow colour appeared immediately, but only the colourless form was recovered. Acid



Methyl pyruvate phenylhydrazones in ether.

A, syn; *B*, anti.

or alkaline hydrolysis of either amide gave the same pyruvic acid phenylhydrazone, identical in infrared absorption with specimens prepared from pyruvic acid and phenylhydrazine in dilute aqueous hydrochloric or acetic acid, alcohol, or ether. The crude materials from these preparations ranged in colour from orange to colourless and in melting point from 170° to 185°, but on purification all gave the compound, m. p. 189°. The presence of an isomeric form in some of these crude acids could not be detected spectroscopically but was shown indirectly by methylation with diazomethane, whereby two isomeric methyl pyruvate phenylhydrazones were obtained. The colourless modification, m. p. 94—95°, is known; [5] the yellow form, m. p. 56—58°, is new. Two isomeric ethyl pyruvate phenylhydrazones, colourless and yellow, melting at 116—117° and 31—32° respectively, have been reported.[6]

It seemed likely that the isomerism of these hydrazones was geometrical. Instances of such isomerism in similar compounds, *e.g.*, acetaldehyde phenylhydrazone [4] and pyruvic acid 2 : 4-dinitrophenylhydrazone,[7] have been observed. The ultraviolet absorption curves

[1] Gastaldi, *Gazzetta*, 1924, **54**, 212.
[2] Leete, Marion, and Spenser, *Canad. J. Chem.*, 1955, **33**, 405.
[3] Abramovitch, *J.*, 1956, 4593.
[4] Cf. Laws and Sidgwick, *J.*, 1911, **99**, 2085.
[5] Simon and Piaux, *Bull. Soc. Chim. biol.*, 1924, **6**, 412.
[6] Simon, *Compt. rend.*, 1900, **131**, 682.
[7] Isherwood and Lumley-Jones, *Nature*, 1955, **175**, 419.

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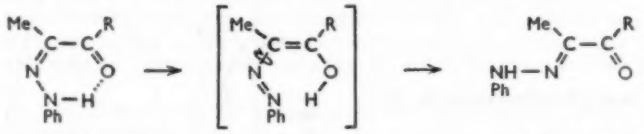
of the isomeric methyl esters (see Figure) show marked differences in the intensity of the band at 295 mμ and, since the more elongated of two geometrical isomers generally shows more intense absorption,[8] the colourless ester, m. p. 94—95° (curve *B*), must have the chromophores *trans* to each other. When the chromophores are *cis* to each other (*syn*-form) hydrogen bonding is possible and this leads to increased resonance energy and therefore to a bathochromic shift of the 315 mμ band to 350 mμ (curve *A*), tailing off into the visible region and giving rise to the yellow colour. We were unable to detect such distinct differences in the ultraviolet spectra of the isomeric amides, presumably owing to the ease with which the *syn*-form isomerises to the *anti*-configuration. A differentiation between the *syn*- (I, II) and *anti*-forms (III, IV) should be possible from a study of the infrared spectra, since the carbonyl group is intramolecularly hydrogen-bonded in the *syn*-form. Chloroform isomerised the yellow to the colourless amide, so that the spectra in this solvent were identical. Examination of potassium chloride discs of the isomeric amides showed that the colourless form had the C=O band at 1681 cm.$^{-1}$, whereas the yellow form had the C=O band at 1656 cm.$^{-1}$, indicating that the carbonyl group is hydrogen-bonded in the yellow form, which is then represented by the *syn*-structure (I). Similarly, the ester-carbonyl band of the high-melting methyl ester occurred at 1698 cm.$^{-1}$ (*anti*), while in the low-melting ester it appeared at 1675 cm.$^{-1}$ (*syn*). The isomerisation, which is probably acid- and base-catalysed, presumably takes place in the stages shown, facilitated in the first instance by the proximity of the oxygen and the hydrogen atom:



(I): R = NH_2
(II): R = OMe

(III): R = NH_2
(IV): R = OMe

There are other differences in the infrared absorption spectra of the two amides. The yellow modification is appreciably soluble in Nujol, giving rise to bands for both solution and mull[3] (Table), whereas the colourless form has the expected three bands in the 3 μ region and the amide I band at 1656 cm.$^{-1}$. Of the two bands exhibited by the yellow form in the 6 μ region, one was previously attributed[3] to a C=N stretching motion. It has now

Infrared bands (cm.$^{-1}$).

Pyruvamide phenylhydrazone:		
yellow form	(*a*) 3509 (sh), 3448, 3300, 3226	1656, 1610
	(*b*) 3534, 3484, 3425, 3322, 3247, 3185 (sh)	1667, 1650, 1608
colourless form	(*a*) 3509, 3356 (sh), 3300, 3247	1681, 1672 (sh), 1613
	(*b*) 3425, 3390, 3236	1656, 1616, 1605 (sh)
	(*c*) 3509, 3413, 3378	1681, 1605
Methyl pyruvate phenylhydrazone:		
yellow form	(*b*) 3279	1675
colourless form	(*b*) 3344	1698, 1667 (sh)
Acetaldehyde phenylhydrazone	(*b*) 3300	1608

(*a*) Potassium chloride disc. (*b*) Nujol mull. (*c*) Chloroform solution.

been observed that acetaldehyde phenylhydrazone itself shows no separate C=N band in this region, but only one band due to both phenyl and C=N absorptions. The coincidence of phenyl and C=N absorptions is in agreement with the observations of Fabian, Legrand, and Poirier,[9] whereas Kirrmann[10] finds that a *NN*-dialkylhydrazone shows a band at 1650 cm.$^{-1}$. It appears that in phenyl(as opposed to alkyl)hydrazones the aryl group

[8] Koch, *Chem. and Ind.*, 1942, **20**, 273.
[9] Fabian, Legrand, and Poirier, *Bull. Soc. chim. France*, 1956, 1506.
[10] Kirrmann, *ibid.*, p. 1751.

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influences considerably the double-bond character of the C=N grouping, perhaps owing to contributions from dipolar canonical forms. It follows that 2 : 3-dioxopiperidine 3-phenylhydrazones should not exhibit the two distinct bands for the amide-carbonyl and the C=N group which were previously expected.[3] The bands at 1667 and 1650 cm.$^{-1}$ in the spectrum of the yellow pyruvamide phenylhydrazone are probably due to C=O absorptions of the compound in solution and in suspension in Nujol.

Experimental

Infrared measurements were carried out on a Grubb–Parsons Model S4 double-beam instrument. Ultraviolet absorption spectra were determined on a Unicam S.P. 500 spectrophotometer.

syn-*Pyruvamide Phenylhydrazone.*—(i) (Cf. ref. 3) Pyruvamide (0·5 g.) in hot water (15 ml.) was treated with phenylhydrazine (0·5 g., 0·46 ml.) in ethanol (2 ml.) and set aside for 15 min. Scratching with a glass rod caused crystallisation of the yellow solid which was collected and recrystallised twice from dilute ethanol, giving yellow needles of the hydrazone, m. p. 118—119° (Found: C, 61·2; H, 6·3; N, 23·4. Calc. for $C_9H_{11}ON_3$: C, 61·0; H, 6·3; N, 23·7%).

(ii) Pyruvamide (0·545 g.) in water (10 ml.) was added to a filtered solution of redistilled phenylhydrazine (0·675 g.) in water (5 ml.) containing acetic acid (0·5 ml.). The mixture became yellow instantly and crystallisation was completed by keeping it at 0° for 2 hr.; the product was collected and recrystallised from dilute alcohol, giving the *syn*-amide phenylhydrazone (0·75 g.), m. p. 117—118°. Concentration of the mother-liquors in the cold at 10^{-3} mm. gave the *anti*-amide phenylhydrazone (0·055 g.), m. p. 143—144°. In more dilute solution a smaller first crop of the *syn*-amide and a larger second crop of the *anti*-amide are obtained.

anti-*Pyruvamide Phenylhydrazone* (cf. Leete, Marion, and Spenser [2]).—Pyruvamide (0·261 g.) in water (2·5 ml.) was added to a warm solution of redistilled phenylhydrazine (0·324 g.) in N-hydrochloric acid (3·5 ml.). The mixture became momentarily yellow, and colourless product separated immediately. After 2 hr. at 0° the product was collected and recrystallised from hot water, giving colourless *anti*-pyruvamide phenylhydrazone (0·435 g.), m. p. 143—144°, $\lambda_{max.}$ 225, 295, 325, mμ (log ε 4·10, 4·05, 4·30) in EtOH (Found: C, 61·1; H, 6·4; N, 23·3%; *M*, 181. Calc. for $C_9H_{11}ON_3$: C, 61·0; H, 6·3; N, 23·7%; *M*, 177). Gastaldi [1] gives m. p. 144°.

Conversion of syn- *into* anti-*Amide.*—Recrystallisation of the *syn*-isomer from water containing 1 or 2 drops of 5N-sodium hydroxide gave the colourless *anti*-isomer, m. p. 143—144°. The same conversion was effected by treating the yellow phenylhydrazone with dilute hydrochloric acid at room temperature or dissolving it in chloroform. A crude sample of the yellow isomer changed to the colourless modification when kept in a specimen tube for a few months.

Treatment of the *anti*-form in aqueous alcohol with sulphur dioxide gave an immediate yellow colour. Evaporation of the solvent gave a yellow product, m. p. 130—135°, but pure low-melting isomer could not be obtained.

Hydrolysis of the Isomeric Amides.—(i) *Acid hydrolysis.* Either amide (0·20 g.) in water (10 ml.) containing a trace of methanol was heated at 100° for 10 min. with 3N-hydrochloric acid (4 ml.); there separated pyruvic acid phenylhydrazone (85%), m. p. 178—179° (decomp.), $\lambda_{max.}$ (log ε in parentheses) 230 (4·05), 295 (4·05) (sh), 320 mμ (4·35) in 0·1N-HCl in aq. EtOH; 290 (4·27), 310 mμ (4·26) in 0·1N-NaOH in aq. EtOH. The infrared spectra of the acids obtained from the *syn*- and the *anti*-amide were identical. If a large excess of hydrochloric acid was used the solution became red and only intractable material was obtained, probably owing to formation of indole compounds.

(ii) *Alkaline hydrolysis.* Either amide (0·3 g.) in hot methanol (4 ml.) was refluxed with 5N-sodium hydroxide (10 ml.). Ammonia was liberated after a few minutes and hydrolysis was complete in 2 hr. The cold solution was acidified with acetic acid, giving pyruvic acid phenylhydrazone, m. p. 180—181° (decomp.), quantitatively. The infrared spectra of the acids obtained were identical with those of the acid hydrolysis products.

Isomeric Methyl Pyruvate Phenylhydrazones.—Redistilled phenylhydrazine (2·7 g.) in ether (30 ml.) was added to pyruvic acid (2·2 g.) in ether (30 ml.) and the phenylhydrazone (2·7 g.), m. p. 178—180° (fraction A), which crystallised almost immediately, was filtered off after the mixture had been kept for 3 days at 0°. The filtrate was taken to dryness and yielded a red solid which was extracted with boiling water (300 ml.), leaving an undissolved residue (0·3 g.), m. p.

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173—174° (fraction B). The aqueous extract gave a further crop of product (0·9 g.), m. p. 179—180°.

(i) anti-*Methyl pyruvate phenylhydrazone*. A suspension of pyruvic acid phenylhydrazone (1 g. of fraction A) in ether was treated with excess of diazomethane in ether. After removal of the solvent the *anti*-ester (0·92 g.) crystallised slowly. It was dissolved in boiling water, filtered from some oily drops, and crystallised in long colourless needles, m. p. 94—95° (Found: C, 62·5; H, 6·5; N, 14·6. Calc. for $C_{10}H_{12}O_2N_2$: C, 62·5; H, 6·3; N, 14·6%). (ii) syn-*Methyl pyruvate phenylhydrazone*. Fraction B was suspended in ether and treated with ethereal diazomethane, the solvent evaporated, and the red oily residue extracted with boiling water. The water-insoluble oil was dissolved in ether, dried (Na_2SO_4), and recovered. The product sublimed at 70°/10^{-3} mm., to give prisms of yellow syn-*methyl pyruvate phenylhydrazone* (0·2 g.), m. p. 56—58° (Found: C, 62·4; H, 6·4; N, 14·5%). At 90°/10^{-3} mm. colourless needles of the *anti*-ester, m. p. 94—95°, sublimed.

We are indebted to Mr. D. M. Adams, of King's College, London, for the preparation of potassium chloride discs of the amides. This work was carried out during the tenure by one of us (R. A. A.) of an I.C.I. Research Fellowship.

King's College, University of London,
Strand, London, W.C.2.
Department of Biochemistry and Chemistry,
Medical College of St. Bartholomew's Hospital,
Charterhouse Square, London, E.C.1. [*Received, March 18th*, 1957.]

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744. *Oxide Film Formation on the Surface of Metals in Aqueous Solutions and the Evaluation of their Standard Potentials. Part V.* The Tin Electrode.*

By (the late) S. E. S. El Wakkad, T. M. Salem, and J. A. El Sayed.

The behaviour of the electroplated tin and tin-amalgam electrodes in solutions of varying pH, initially free from tin ions, is examined from the extreme acid to the extreme alkaline range, and the probable existence of an oxide film on the surface of metals discussed. A new technique is described for measuring the potential of tin out of contact with air.

By comparing the results obtained in such solutions in and out of contact with air a set of conditions was chosen leading to the evaluation of the true standard electrode potential. That for tin was thus found to be −0·1375 v at 25°, compared with the value of −0·1364 v in air.

In our previous investigations [1] an oxide was found to exist on the surface of metals in aqueous solutions. The effect of this film on the thermodynamic potential of the electrode has been discussed and a new technique introduced for measuring the standard potential of these metals out of contact with atmospheric oxygen (*i.e.*, under conditions such that no film exists).

The present investigation deals with metallic tin, concerning which the limited work already reported [2,3] is conflicting. We have studied the growth of an oxide film on tin, and the behaviour of the electrode over a wide pH range in the presence and absence of air and after removal of the oxide film, and have thus determined the true standard electrode potential.

* Part IV, *J. Egypt. Acad.*, 1956, No. 12, 7.

[1] Tourky and El Wakkad, *J.*, 1948, 740; El Wakkad and Salem, *J. Phys. Colloid Chem.*, 1950, **54**, 1371; Electrochem. Soc. Meeting, Cincinnati, Ohio, May, 1955, p. 60; El Wakkad, Salem, and El Ghandour, *J. Egyptian Acad.*, 1956, No. 12, 7, in the press.

[2] Hoar, *Trans. Faraday Soc.*, 1937, **33**, 1152; Haring and White, *Trans. Electrochem. Soc.*, 1938, **73**, 11.

[3] Noyes and Toabe, *J. Amer. Chem. Soc.*, 1917, **39**, 1537.

Experimental

Tin Electrodes.—Tin electrodes were prepared by electrodeposition from a solution of stannous chloride dihydrate (2·8 g.) in 2N-sodium hydroxide (40 c.c.) at 2 mA/electrode for 10 min. at 80° on a platinum wire 1 cm. long and 0·1 cm. in diameter. The electrode was washed several times with conductivity water, then with the solution in which the measurements were carried out.

For preparation of tin-amalgam electrodes a similar platinum wire was electroplated with mercury at 3 mA/electrode for 30 min. from dilute nitric acid saturated with mercurous nitrate at 25°. The electrode was washed several times with conductivity water, then electroplated with tin as just described. A fresh plating was used for each experiment.

Buffer Solutions.—These covered the pH range 1·0—11·36, as follows: pH 1·0—2·2, solutions prepared from hydrochloric acid and potassium chloride;[4] pH 3·61—5·63, acetic acid—acetat;[5] pH 6·77—9·24, boric acid–borax;[6] pH 10·17—11·36, sodium carbonate–hydrochloric acid.[7] For the extreme acid and alkaline ranges hydrochloric acid and sodium

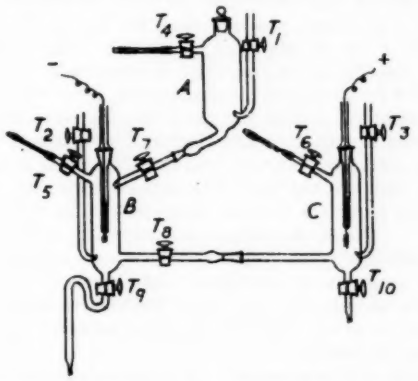

Fig. 1. *Apparatus for measurements out of contact with air.*

hydroxide solutions were used. All solutions were prepared from highly purified materials and their pH values checked with the hydrogen electrode and, when possible, with the quinhydrone electrode.

Preparation of Electrodes and Solutions for Measurements out of Contact with Air.—For this an electrochemical method was based upon our studies of the anodic behaviour of tin.[8] It consisted of cathodic reduction of tin or tin amalgam in the solution in which the measurements were carried out, all operations being carried out in an atmosphere of nitrogen (from cylinders and purified as recommended by Harcourt and Lupton [9]). The apparatus is shown in Fig. 1. The cell resembled that used for mercury.[10] Its three compartments *A*, *B*, and *C* were fitted to each other by very tight ground joints. Taps 1, 2, and 3 were for the inlet of nitrogen, and 4, 5, and 6 for outlet. Taps 7 and 8 served for transference of the solutions from one compartment to the other, and taps 9 and 10 for their discharge. The cathode present in compartment *B* was a platinum plate of surface area 1 sq. cm., electroplated with tin or tin amalgam as described above. The anode in compartment *C* was a platinum spiral 5 cm. long and 0·1 cm. thick. The solutions used were boiled and cooled in an atmosphere of pure nitrogen and introduced into compartment *A*, then were allowed to pass through *B* and *C*. The tin electrode was reduced cathodically with a polarising current of about 6 mA/electrode for about an hour, in an atmosphere of pure nitrogen which was allowed to bubble through the solution present even in the anode compartment *C* to remove the oxygen evolved and prevent its diffusion into

[4] Clark and Luba, cited in Britton's "Hydrogen Ions," Chapman and Hall, London, 1932, p. 301.
[5] Cohn, *J. Amer. Chem. Soc.*, 1927, **49**, 173.
[6] Palitzsch, cited in Britton's "Hydrogen Ions," see ref. 4, p. 219.
[7] Kolthoff, cited in Britton's "Hydrogen Ions," see ref. 4.
[8] El Wakkad, El Din, and El Sayed, *J.*, 1954, 3103.
[9] Harcourt and Lupton, *J. Chem. News*, 1876, **33**, 90.
[10] El Wakkad and Salem, *J. Phys. Chem.*, 1952, **56**, 621.

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the solution in the cathode compartment *B*. After complete cathodic reduction taps, 2, 5, 7, 8, and 9 were closed and the cathodic compartment *B* was released from the other two compartments to be connected through the tap 9 to the reference half-cell which was either the saturated calomel electrode (when examining the electrode behaviour in solutions free from tin ions) or a hydrogen electrode (when determining the standard electrode potential). The pH value of each solution used was checked directly before and after electrolysis and never varied by more than 0·08 pH unit after electrolysis.

Stannous Perchlorate.—This was prepared as recommended by Noyes and Toabe,[3] *i.e.*, indirectly. " AnalaR " cupric oxide was dissolved in an excess of boiling diluted " AnalaR " perchloric acid, individual dilutions being standardised against sodium carbonate. Then tin shavings were added in large excess. The copper separated completely as a spongy deposit, leaving a colourless solution of stannous perchlorate, which was filtered through asbestos in an atmosphere of carbon dioxide and in contact with metallic tin, and kept in glass-stoppered bottles filled with carbon dioxide and containing metallic tin. From this stock solution various dilutions were prepared and used within 12 days. During this period the conductance of the stock solution was determined every 2 days in an evacuated conductivity cell; the conductance remained constant, showing that the ion concentration did not change during this period in spite of the development of a yellow colour; the solution remained clear. The molarity of ten perchlorate in the stock solution was determined by titration under carbon dioxide against 0·1N-potassium permanganate, after further acidification with 20% perchloric acid. Free perchloric acid in the stock solution was determined by diluting a weighed portion and saturating it with hydrogen sulphide; after the tin sulphide has settled, it was filtered off and washed until free from acid, and the filtrate was boiled for 20 min. to remove hydrogen sulphide, cooled, and titrated with 0·1N-sodium hydroxide to phenolphthalein; subtracting from the acid thus found the number of equivalents of tin present gave the quantity of free acid in the solution. The stock solution was analysed for both perchlorate and free perchloric acid before every dilution. The results obtained were always in satisfactory agreement with each other.

The molarity of perchloric acid chosen varied between 0·05 and 0·005M, while those of stannous perchlorate were from 0·016999 to 0·000212M. However, this variation lies within the range of pH in which the potential measurements with a tin electrode are not contaminated by oxide formation.

Electrical Measurements.—The measurements were carried out in duplicate with different stock solutions. In the buffer solutions the measurements were performed with a saturated calomel electrode as the reference half-cell. The procedure suggested by Harned and Owen [11] was used, and the experimental E_0 pH value of our saturated calomel electrode, determined in buffers with acids of known dissociation constants and after the necessary corrections, was taken as 0·245 v at 25°. The cells were kept in an air-thermostat at 25° ± 0·02°.

The e.m.f. measurements were carried out with a calibrated metre bridge on which accurate readings could be taken to 0·02 cm. A cadmium cell calibrated by the National Physical Laboratory and an Onwood mirror galvanometer having a sensitivity of 190 mm./10^{-6}A were used.

Results and Discussion

Behaviour of the Electrode in Solutions of Various pH, *initially containing no Tin ions, in Air.*—The potential–pH curves (Figs. 2*A* and 3*A*) for the electroplated tin electrodes and tin-amalgam electrodes respectively in unstirred solutions of varying pH, show that the potential of both types of electrodes varies linearly with the logarithm of the hydrogen-ion activity of the solution from pH 5 to 11 for the former electrode and from pH 3·6 to 11 for the latter. For the extreme acid region and the extreme alkaline region the potential values of such electrodes deviate, however, from the theoretical for the hydrogen electrode. The values obtained in the acid region for the tin-amalgam electrode are more positive than those of the electroplated tin electrode. From pH 11 to 12·6 both electrodes show irregular variation in potential. The $E_H{}^0$ values for the tin and the amalgamated-tin electrode are 0·065 and 0·075 v respectively. Curves *B* in Figs. 2 and 3 show the theoretical curve for $Sn(OH)_2/Sn(OH)_4$ while curves *C* in the same figures are for $Sn/Sn(OH)_2$.

[11] Harned and Owen, " Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1943, p. 311.

The behaviour of metals which show a potential varying linearly with pH is usually attributed to the formation of an oxide film on the surface of the metal (El Wakkad *et al.*[1]), and thus the electrode behaves as a metal–metal oxide electrode.

To ascertain which type of oxide is formed one must calculate from the thermal data the potentials of the different oxides of tin to see which of them agrees with the experimental results. If the free energy of $Sn(OH)_2$ is taken as −115,200 cal. and that of OH^- as −37,585 cal.,[12] the free energy change of the reaction, $Sn + 2OH^- = Sn(OH)_2 + 2e$, is $\Delta F = -40{,}030$ cal. This gives an E_B^0 value (potential values at the extreme alkaline range of pH) of −0·87 v at 25°. Applying the ordinary equation for the variation of the potential of a metal–metal oxide electrode with the pH, we obtain E_H^0 for the Sn–$Sn(OH)_2$

FIG. 2.

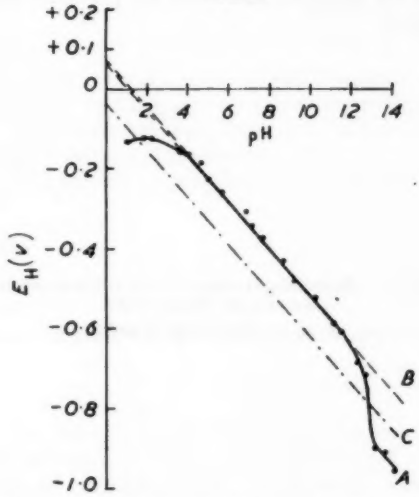
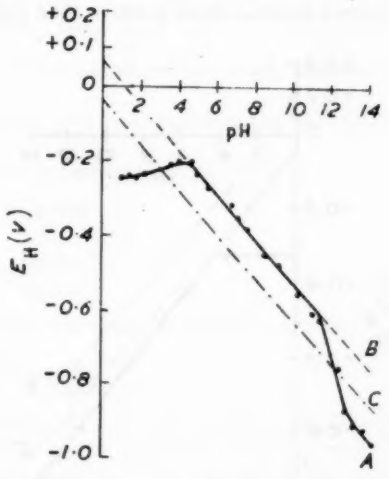


FIG. 3.



FIGS. 2 and 3. *Potential–pH curves for (Fig. 2) tin-amalgam and (Fig. 3) tin electrodes, in presence of air.*

A, Experimental values. B, Theoretical values for $Sn(OH)_2/Sn(OH)_4$. *C, Theoretical values for* $Sn/Sn(OH)_2$.

electrode a value of −0·05 v. Taking the free energy of formation of stannic hydroxide as −226,000 cal. gives the free-energy change of the reaction, $Sn(OH)_2 + 2OH^- = Sn(OH)_4 + 2e$, as −35,630 cal. and thence $E_B^0 = -0{\cdot}77$ v, so that E_H^0 is +0·05 v.

This indicates that $Sn(OH)_4$ is formed on the surface of metallic tin in aqueous solutions in air and that this oxide is responsible for the linearity in the potential pH curve.

For the region in the potential–pH curve from pH 11 to 12·6, the irregularity can be attributed to the probable amphoteric character of stannic hydroxide. However, this break corresponds actually to the region of the isoelectric point of such a hydroxide,[13] and analogous findings have been made before in this laboratory.

In the acid range the lack of linearity for both electrodes can be attributed to the primary formation, on the surface, of stannous hydroxide which tends to saturate the double layer; owing to the great solubility of the oxide in such solutions, this will lead

[12] Latimer, "The Oxidation States of Elements and their Potentials in Aqueous Solutions," Prentice-Hall, New York, 1938, p. 199.
[13] Dey and Ghosh, *Proc. Nat. Inst. Sci. India*, 1946, **15**, *A*, 143.

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to variation in the pH of the solution at the interphase, causing it to increase so that the potential will be lower than expected. The local change of pH in the vicinity of the electrode was found previously for mercury [14] and tungsten.[15] This is confirmed for the present case when the results obtained with tin and tin-amalgam electrodes are compared: the latter, being more protected, give more positive potential values.

From pH 12·6 to the extreme alkaline range the potential value deviates from the theoretical one for the hydrogen electrode. It is suggested that in this region stannous hydroxide, when first formed on the surface of the electrode, dissolves freely giving stannite which is unstable and decomposes to stannate. The free-energy change of the reaction, $Sn + 6OH^- = Sn(OH)_6^{2-} + 2e$, is $\Delta F = -80{,}490$ cal. and so E_B^0 is $-1{\cdot}74$ v, which is a very negative potential value when compared with the potential obtained, $-0{\cdot}96$ v. This suggests that, in alkaline solutions, owing to dissolution of stannous oxide, the hydroxyl-ion concentration decreases in the vicinity of the electrode, and hence the potential value measured becomes more positive than expected.

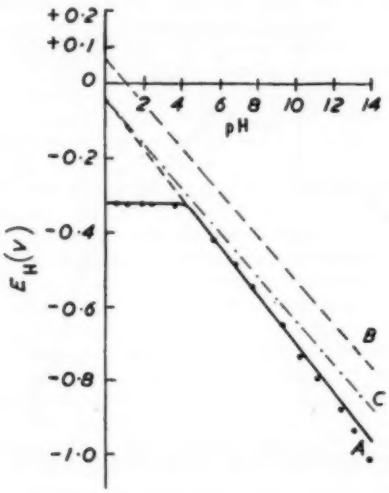

FIG. 4. *Potential–pH curves for tin or tin-amalgam electrodes, in absence of air.*
A, B, C, As for Figs. 2 and 3.

Behaviour of the Electrode in Solutions of Various pH, *initially containing no Tin Ions, out of Contact with Air.*—To remove the oxide from the surface of the electrode and eliminate the effect of atmospheric oxygen, the tin electrode was reduced electrolytically as described above. Fig. 4 shows the variation of the potential of both the electrochemically reduced tin and the tin-amalgam electrode with the pH of the solution. In solutions having pH >4·5, these potentials are a linear function of the pH. The E_H^0 value for this portion of the curve was $-0{\cdot}040$ v. The linearity was due to the formation of stannous oxide, and this value found is in good agreement with the theoretical value previously calculated. At the extreme alkaline region (pH 13 and 14) the negative potential values obtained are due to the formation of stannate. The formation of an oxide film on the surface of metals out of contact of air, in comparatively alkaline solutions, can be attributed to the increase of hydroxyl-ion concentration: a state is expected to be reached where hydroxyl ion together with the metal ions present will saturate the interphase with the metal hydroxide so that the metal starts to function as a metal–metal oxide electrode.

From pH 1 to 4·5 the potential constant for both electrodes is about $-0{\cdot}320$ v. When

[14] El Wakkad and Salem, *J. Phys. Chem.*, 1952, **56**, 621.
[15] El Wakkad, Rizk, and Ebaeid, *ibid.*, 1955, **59**, 1004.

a pure metal is dipped in an aqueous solution containing no ions of this metal, and in absence of dissolved oxygen which may act as electron acceptor, the potential of this metal in the comparatively acid solution is expected to be extremely negative, leading to dissolution of the metal and discharge of hydrogen ions. The potential observed in this case is expected to be governed by the potential of the hydrogen electrode at the corresponding pressure and the pH prevailing within the double layer, and also by the hydrogen overpotential on the particular metal. This indicates the absence of any oxide film from the surface of the metal from the extreme acid range of pH to about pH 5 in solutions freed from dissolved oxygen. The evaluation of the standard electrode potential of tin under these conditions in solutions of pH values less than 5 will therefore give the exact thermodynamic reversible value.

Evaluation of the Standard Potential of Tin.—The cell used was of the type :

H_2	$HClO_4$ (xM)	$HClO_4$ (xM)	Sn
		$Sn(ClO_4)_2$(yM)	

y was made small compared with x, so that the two solutions became nearly identical and the liquid junction potential became negligible.

Measurements were made out of contact with air, and for comparison the same cell was studied without this extreme protection.

The reaction taking place in the tin half-cell can be expressed as :

$$H_2 + Sn^{2+} = Sn + 2H^+$$

Thus

$$E = E_0 - \frac{RT}{2F} \log \frac{a_{Sn} a_{H^+}{}^2}{a_{H_2} a_{Sn^{2+}}}$$

Since tin and hydrogen are at their standard states this equation at 25° reduces to :

$$E = E_0 - \frac{0{\cdot}0591}{2} \log \frac{a_{H^+}{}^2}{a_{Sn^{2+}}}$$

For calculation of the standard electrode potential, it is only necessary to determine the activity of H^+ in the hydrogen half-cell and that of Sn^{2+} in the tin–stannous perchlorate half-cell. Following the procedure of Lewis and Randall [16] for calculating the activity coefficient of various ionic strengths gives the E_0 values for unprotected and protected electrodes shown in the Table. The E_0 value obtained in air is −0·1364 v, and that out of contact with air is −0·1375 v, which is the true standard electrode potential of tin. The maximum error in our measurements is ±0·0005 v.

$HClO_4$ (M)	$Sn(ClO_4)_2$ (M)	E_0 (in air) (V)	E_0 (V)	$HClO_4$ (M)	$Sn(ClO_4)_2$ (M)	E_0 (in air) (V)	E_0 (V)
0·05	0·016999	−0·1363	−0·1373	0·005	0·000849	−0·1367	−0·1378
0·05	0·008499	−0·1370	−0·1370	0·005	0·000424	−0·1368	−0·1374
0·05	0·004249	−0·1369	−0·1370	0·005	0·000212	−0·1362	−0·1376
0·01	0·003399	−0·1361	−0·1378				
0·01	0·001699	−0·1360	−0·1377				
0·01	0·000849	−0·1362	−0·1375				

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Cairo University, Faculty of Science, Cairo, Egypt.
Ein Shams University, University College for Girls, Cairo, Egypt.

[*Received, January 17th*, 1957.]

[16] Lewis and Randall, " Thermodynamics and the Free Energy of Chemical Substances," McGraw-Hill, New York, 1923, p. 334.

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745. *Oxide Film Formation on the Surface of Metals in Aqueous Solutions and the Evaluation of their Standard Potentials. Part VI.* The Tungsten Electrode.*

By (the late) S. E. S. El Wakkad, T. M. Salem, H. A. Rizk, and J. G. Ebaid.

Apparatus and technique are described for measuring the potential of a tungsten electrode in solutions of varying pH and initially free from tungsten ions. The true standard electrode potential, thus evaluated, is −1·0069 v at 25°.

The electrochemical behaviour of the tungsten electrode, in solutions of different pH values, is known [1] to depend upon whether it is in the massive or powdered form. The pH range has been determined over which it functions as an indicator electrode for hydrogen-ion activity. Electrodes which show potentials varying linearly with the pH of the solution are usually considered to contain an oxide film on the surface of the metal,[2] and this has been confirmed for the tungsten–tungsten trioxide electrode, the tungsten-blue electrode, and the anodic oxidation of tungsten at very low current density.

In this present investigation a technique has been developed for removal of the oxide film from tungsten and its true thermodynamic standard electrode potential has been determined.

Experimental

Electrodes.—Tungsten rod was cleaned with concentrated sodium hydroxide solution, rubbed with very fine emery paper till its surface was bright, washed with previously boiled and cooled conductivity water, and dried with filter paper.

Solutions.—These were as in Part V of this series.[3]

Preparation of Electrodes and Solutions for Measurements out of Contact with Air.—(a) *Chemical reduction with hydrogen at a high temperature.* The apparatus (Fig. 1) consisted of the tungsten rod electrode of diameter 0·4 cm. and length 5·5 cm., ground at one end for a distance of 1·5 cm. so that it fitted tightly in the ground end *P* of a silica tube when the apparatus was tilted vertically. The silica tube, 28 cm. long, was fitted by ground joints to two soda-glass tubes *A* and *B*. The joint *A* formed part of a small jacket, at the bottom of which a platinum wire spiral *R* was sealed to provide a connection between the electrode and the outer circuit, the connection being completed by mercury in the side tube, into which a bright copper wire electrode dipped. The spiral *R* was made in such a way that when the device was moved to the vertical position, the rod fitting tightly in *P*, also fitted conveniently into *R*. The silica tube was placed in an electric oven, then fitted with the jackets *A* and *B* with high-temperature grease and heated to remove the volatile components. The apparatus was then sealed at *D* to a high-vacuum pump and drawn out there to form a capillary constriction. The joint *B* was connected to another joint *O* ending in a sealed capillary tube *C*. When a high vacuum was attained pure hydrogen was introduced into the system. This evacuation and filling with hydrogen were repeated 3 times before the electrode was heated. Pure hydrogen introduced the third time was at a pressure of 1·2 atm. and the rod was then heated for 1 hr. at about 950°. Heating was then stopped and evacuation was carried out while the electrode was gradually cooling. When a high vacuum was attained and the temperature of the electrode reached room temperature the apparatus was sealed at *D* and tilted vertically, then fitted tightly into an electrode vessel similar to that used for mercury.[2b] The capillary tube *C* was broken, and the solution present in the electrode vessel thus admitted to the electrode jacket.

* Part V, preceding paper.

[1] El Wakkad, Rizk, and Ebaid, *J. Phys. Chem.*, 1955, **59**, 1004; El Wakkad and Rizk, *ibid.*, 1957, **61**, 494.

[2] (*a*) Tourky and El Wakkad, *J.*, 1948, 740; (*b*) El Wakkad and Salem, *J. Phys. Colloid Chem.*, 1950, **54**, 1371; (*c*) Electrochem. Soc. Meeting, Cincinnati, Ohio, 1955, p. 60; El Wakkad, Salem, and El Ghandour, *J. Egyptian Acad.*, 1956, No. 12, 7.

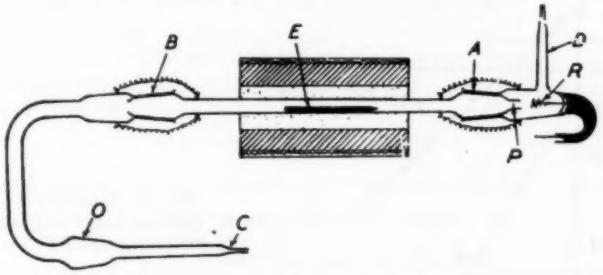
[3] Preceding paper.

(b) *Electrolytic reduction.* This method was based upon cathodic reduction of tungsten in strong alkali hydroxide solution, without exposure of the electrode to oxygen. The cathode was a tungsten rod 3 cm. long and 0·3 cm. thick and the anode was a platinum spiral 5 cm. long and 0·1 thick. Each electrode was sealed in a Pyrex glass tube, ground on the outside so that it fitted into an apparatus similar to that used for mercury [4] and tin. Reduction was carried out in pure nitrogen, which bubbled through the anode compartment to remove the oxygen evolved and prevent it from diffusion into the cathode compartment.

Solutions used for the determinations were freed as far as possible from dissolved oxygen by bubbling pure nitrogen into them. The hydrogen and nitrogen supplied from cylinders were purified as recommended by Noyes [5] and by Harcourt and Lupton [6] respectively. Measurements were carried out in an air-thermostat at 25° ± 0·02°. The reference half-cell was a saturated calomel electrode (for solutions free from tungsten ions) or a hydrogen electrode (when determining the standard electrode potential).

Sodium Hydroxide Solutions.—" AnalaR " sodium hydroxide was dissolved in about its own weight of conductivity water, transferred to a Pyrex glass tube lined with paraffin wax,

FIG. 1. *Apparatus for reduction of tungsten electrode by hydrogen at* 950°.



and left for several days to allow carbonate to settle. The clear supernatant solution was transferred in an atmosphere of pure nitrogen to the dilution apparatus described by Vogel.[7] Dilutions prepared from this solution were standardised against hydrochloric acid.

Sodium Tungstate Solutions.—From " AnalaR " anhydrous sodium tungstate solutions of known molarities were prepared by weight, and their strengths checked by means of the benzidine reagent.[8]

Electrical Measurements.—These were made in duplicate with independent stock solutions. The reference half-cell was the saturated calomel electrode whose potential with the liquid junction potential was 0·2448 v at 25°. E.m.f. measurements were carried out with a calibrated metre bridge similar to that used for mercury and tin.

RESULTS AND DISCUSSION

Measurements were made in a cell of the type :

$$W \text{ (reduced in absence of } O_2) \mid \text{Buffer—satd. KCl—KCl, } Hg_2Cl_2 \mid Hg$$

When the rod tungsten electrode was heated at 950° in hydrogen and then in a high vacuum, and then examined in oxygen-free buffer solutions the potential of the electrode was still a linear function of the pH of the solution. The E_H^0 values was 0·15 (see from Fig. 2*A*), indicating that heating the tungsten electrode in hydrogen at 950° reduces the tungsten trioxide only to the intermediate product, tungsten blue.[1]

Fig. 2*B* shows that the potential of electrochemically reduced tungsten is constant from the extreme alkaline pH to about 11. Throughout this range the potential of the electrode in complete absence of oxygen is about −0·92 v, the reproducibility within this

[4] El Wakkad and Salem, *J. Phys. Chem.*, 1952, **56**, 621.
[5] Noyes, *J. Amer. Chem. Soc.*, 1907, **29**, 1718.
[6] Harcourt and Lupton, *J. Chem. News*, 1876, **33**, 90.
[7] Vogel, " Quantitative Inorganic Analysis," Longmans, Green and Co., London, 1939, p. 286.
[8] *Idem, op. cit.*, 1948, p. 575.

range of pH being of the order of 12 mv. This value is not in agreement with the calculated values [1] of E_B^0 of any of the oxides of tungsten (WO_2, W_2O_5, WO_3). At such extreme ranges of pH one must also expect that oxides of tungsten possess higher solubilities, if ever formed on the surface of the electrode. In solutions with pH values lower than 11 the protected electrode began to show potentials which varied linearly with pH. However, the slope of curve *B* is greater than that expected for an electrode acting as a pH indicator. This is in accordance with findings by El Wakkad *et al.*[1] and Baylis.[9] Antimony electrodes, which act as hydrogen electrodes, behave similarly.[10] The E_H^0 value was −0·05 v, in good agreement with the value calculated from the reaction: $W + 2H_2O = WO_2 + 4H^+ + 4e$.

Evaluation of the Standard Potential of Tungsten.—For this determination the tungsten electrode was reduced cathodically in a strongly alkaline solution. The standard electrode potential of tungsten–tungstate ion was determined in alkaline hydroxide solutions where the tungsten electrode is not covered with an oxide film; further, in these strong solutions

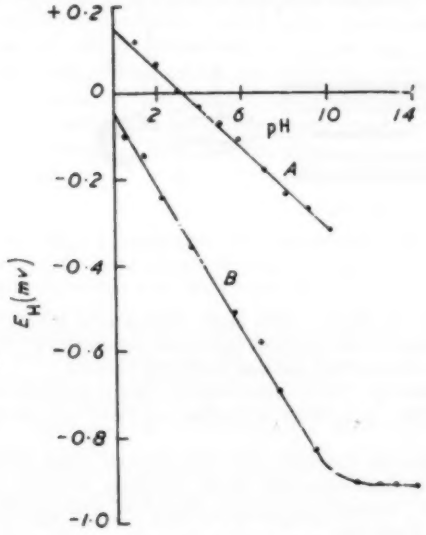


FIG. 2. *Voltage–pH curves.*
A, Electrode heated in hydrogen.
B, Electrode reduced electrochemically.

there will be no tendency for the formation of polytungstate.[11] There is no previous determination of such standard electrode potentials and only an approximate value based on thermal data was given by Latimer.[12] The cell was of the type:

$$H_2 \mid x\text{M-NaOH}, x\text{M-NaOH} + y\text{M-}Na_2WO_4 \mid W$$

y being small compared with x, the two solutions became nearly identical and the liquid junction potential became negligible. Measurements were made out of contact with air. The reaction taking place in the tungsten half-cell can be represented as:

$$WO_4^{2-} + 4H_2O + 6e = W + 8OH^-$$

In the case of the hydrogen half-cell, the reaction taking place is:

$$H_2 - 2e = 2H^+$$

[9] Baylis, *Ind. Eng. Chem.*, 1923, **15**, 852.
[10] El Wakkad, *J.*, 1950, 2894; Parks and Beard, *J. Amer. Chem. Soc.*, 1932, **54**, 856; Perley, *Ind. Eng. Chem. Anal.*, 1932, **54**, 856.
[11] El Wakkad and Rizk, *J. Phys. Chem.*, 1957, **61**, 494.
[12] Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solutions," Prentice-Hall, New York, 1938, p. 237.

Since tungsten and hydrogen are at their standard states, it is only necessary for calculating the standard electrode potential at W/WO_4^{2-} to determine the activity of the hydrogen ion in the hydrogen half-cell and that of the tungstate ion in the W/WO_4^{2-} half-cell. By following the procedure of Lewis and Randall [13] for calculating the activity coefficient at

NaOH (M)	Na_2WO_4 (M)	E.m.f. (V)	E_0 (V)	NaOH (M)	Na_2WO_4 (M)	E.m.f (V)	E_0 (V)
0·1	0·01	0·1672	−1·0086	0·025	0·00020	0·1592	−1·0075
0·1	0·005	0·1564	−1·0061	0·025	0·00010	0·1499	−1·0069
0·1	0·0025	0·1478	−1·0058	0·025	0·00005	0·1408	−1·0067
0·05	0·00125	0·1609	−1·0063				
0·05	0·00100	0·1595	−1·0078				
0·05	0·00050	0·1498	−1·0069				

various ionic strength, the standard electrode potential of W/WO_4^{2-} was calculated and is given in the Table: the mean value is $-1·0069 \pm 0·0004$ v at 25°, as compared with value of −1·1 v obtained by Latimer [12] from thermal data.

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CAIRO UNIVERSITY, FACULTY OF SCIENCE, CAIRO. [*Received, January 17th*, 1957.]
EIN SHAMS UNIVERSITY, UNIVERSITY COLLEGE FOR GIRLS, CAIRO, EGYPT.

[13] Lewis and Randall, "Thermodynamics and the Free Energy of Chemical Substances," McGraw-Hill, New York, 1923, p. 334.

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746. *Constituents of the Lipids of Tubercle Bacilli. Part VIII.* Studies on Mycolic Acid.*

By E. D. MORGAN and N. POLGAR.

A scheme for a stepwise degradation of mycolic acid is presented. Oxidation of methyl anhydromycolate, obtained *via* the toluene-*p*-sulphonyl ester of methyl mycolate, with potassium permanganate in acetone gave *n*-pentacosanoic acid together with a methoxy-acid, named *O*-methylmeromycolic acid, having 26 carbon atoms less than the parent acid. Demethylation of this methoxy-acid with acetic anhydride and toluene-*p*-sulphonic acid afforded an acetoxy-acid which, on pyrolysis of its methyl ester, yielded an unsaturated ester. This ester on oxidation with potassium permanganate in acetone is shown to give a straight-chain acid, presumed to be heptadecanoic acid, and the half-ester of a branched-chain dicarboxylic acid. The structural features of mycolic acid in the light of the present and of earlier results are discussed.

MYCOLIC ACID was isolated from the wax fractions of human tubercle bacilli (strain H 37) by Stodola, Lesuk, and Anderson; it was assigned the formula $C_{88}H_{176}O_4$ and shown to contain one carboxyl, one hydroxyl, and one methoxyl group.[1] Asselineau and Lederer,[2] in examining samples of mycolic acid from different strains of human tubercle bacilli, found variations in the composition and physical properties of the products. In these studies they subjected the crude acids to chromatography over alumina and found that small amounts of the material were more strongly adsorbed than the main component, and had different m. p.s. They distinguished the products by Greek-letter prefixes indicating the order of elution and designated the acid which was first eluted α-mycolic acid. Most of the acids isolated from human strains (those from other strains are not considered here)

* Part VII, *J.*, 1956, 2036.

[1] Stodola, Lesuk, and Anderson, *J. Biol. Chem.*, 1938, **126**, 505; Lesuk and Anderson, *ibid.*, 1940, **136**, 603.

[2] For a general review see Asselineau and Lederer, *Fortschr. Chem. org. Naturstoffe*, 1953, **10**, 170, and references cited there.

were shown by Asselineau and Lederer to undergo, in agreement with earlier findings,[1] pyrolytic decomposition with the formation of *n*-hexacosanoic acid; dehydration with a mixture of acetic anhydride and potassium hydrogen sulphate gave an αβ-unsaturated acid, named anhydromycolic acid. From these facts together with other evidence, including the isolation of *n*-pentacosanoic acid on ozonolysis of anhydromycolic acid (from α-mycolic acid, m. p. 55—56°, isolated from the strain "Test"), the French investigators inferred that mycolic acid from human tubercle bacilli contains a *n*-tetracosyl branch in α-position and a hydroxyl group in β-position to the carboxyl group.[3]

The acid studied in the present work was obtained from human tubercle bacilli (strains D.T., P.N., and C.[4]) in the course of investigations earlier described.[5] It had, after purification by precipitation of its benzene solution with methanol, m. p. 54—55°. Chromatography over alumina resulted in loss of material, the recovered acid (about 80%) showing no change of m. p. When the corresponding methyl ester, m. p. 43—44·5°, was subjected to chromatography over alumina, most of the material was recovered with the same m. p., except the most strongly adsorbed portion (about 7%) which had a lower m. p., but showed no difference in its infrared spectrum. In agreement with earlier statements the acid, hereafter called simply mycolic acid, was found to contain one carboxyl, one hydroxyl, and one methoxyl group, and gave on pyrolysis hexacosanoic acid.

The infrared spectra of mycolic acid and methyl mycolate (paraffin mulls or natural films) show bands at 3484 (bonded hydroxyl) and 1094 cm.$^{-1}$ (alkyl ether). The carbonyl stretching band appears at 1681 cm.$^{-1}$ (shoulder at 1706 cm.$^{-1}$) for the acid, and at 1709 cm.$^{-1}$ (shoulder at 1730 cm.$^{-1}$) for the ester, *i.e.*, at lower frequencies than usually associated with saturated acids and esters, presumably owing to hydrogen-bonding between the carbonyl and hydroxyl group (cf. Gordy [6]); the spectrum of the acetyl derivative of methyl mycolate shows the normal value of 1742 cm.$^{-1}$.

Chemical studies of mycolic acid are complicated by the fact that degradation products of comparable size differ but little in physical properties, and it is difficult to separate the desired product from any unchanged starting material or from by-products; moreover, there is a lack of reliable criteria for the homogeneity of such substances. With these difficulties in mind we adopted the following scheme which permitted a systematic breakdown of mycolic acid, and the isolation of the resulting degradation products.

We decided to convert mycolic acid into methyl anhydromycolate, and to oxidise the latter with potassium permanganate in acetone. If there were any saturated esters (including unchanged methyl mycolate) present, they would not interfere, since these esters are unaffected by potassium permanganate in acetone; any acidic products obtained would, therefore, represent oxidation products of methyl anhydromycolate. We were aware of the difficulties to be expected in attempting to separate the acidic oxidation products from non-acid material by the usual procedures, but such separations can be readily achieved by taking advantage of the retention of acidic products by the manganese dioxide precipitate resulting on oxidation with potassium permanganate in acetone. The opportunity is taken to point out the general usefulness of this procedure, already employed in an earlier case, namely, for the oxidation of methyl mycolipenate, but only mentioned in the Experimental section of the paper.[7] Small amounts of manganese dioxide can absorb appreciable quantities of acidic oxidation products, and the latter are readily liberated on dissolving the manganese dioxide (after being washed to remove non-acid material), *e.g.*, by the addition of aqueous sodium hydrogen sulphite and hydrochloric acid. The presence of any water-insoluble acidic oxidation products is immediately seen after the manganese dioxide has dissolved, and even small amounts can thus be readily detected.

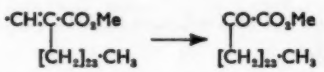
[3] Ref. 2, p. 198.
[4] Green, *Veterinary J.*, 1946, **102**, 267.
[5] Chanley and Polgar, *J.*, 1954, 1003.
[6] Gordy, *J. Chem. Phys.*, 1940, **8**, 516.
[7] Polgar, *J.*, 1954, 1008.

XUM

The first step was the preparation of methyl anhydromycolate. Attempts to dehydrate mycolic acid by means of acetic anhydride and potassium hydrogen sulphate under the conditions previously described [8] gave low yields of αβ-unsaturated material, and also resulted in partial loss of the methoxyl group (see also Asselineau [9]). In our work the toluene-*p*-sulphonyl derivative of methyl mycolate, obtained by reaction of methyl mycolate with toluene-*p*-sulphonyl chloride in pyridine, was heated with benzene–methanolic potassium hydroxide (cf. Linstead *et al.*;[10] Pudles and Lederer [11]); acidification then readily gave a product which, as indicated by its ultraviolet absorption (ε 12,700 at 2180 Å), characteristic of an αβ-unsaturated acid, was essentially anhydromycolic acid. This with diazomethane gave the methyl ester which was oxidised with potassium permanganate in acetone.

In preliminary experiments the resulting manganese dioxide precipitate, after being washed with acetone, was still contaminated with appreciable amounts of neutral material, owing to the sparing solubility of the latter in acetone. Attempts to separate it from the acidic material by chromatography resulted in considerable loss of acids. It was then found that the non-acid material could be satisfactorily removed by refluxing the manganese dioxide with ether, then centrifuging the ethereal suspension to separate colloidal manganese dioxide. Further, it was found advantageous to introduce the potassium permanganate gradually from a Soxhlet apparatus.

The non-acid material isolated after the oxidation appeared to consist only of methyl mycolate and a little methyl anhydromycolate. Treatment of the acidic product, obtained from the manganese dioxide precipitate, with urea [12] removed pentacosanoic acid as a complex, and left a branched-chain methoxy-acid, now named *O*-methylmeromycolic acid. Methyl 2-oxohexacosanoate which might be expected to arise on oxidation of methyl anhydromycolate according to the scheme



has been found [13] to be oxidised to pentacosanoic acid under the conditions employed.

O-Methylmeromycolic acid, which in the above experiments resulted from mycolic acid by the loss of twenty-six carbon atoms, distilled unchanged in a high vacuum at about 300°. This thermal stability appeared to rule out the presence of an α-methoxyl group since an α-methoxy-acid should give an aldehyde of one carbon atom less at the high temperature required for the distillation (cf. Darzens and Levy [14]). Moreover, the methoxyl group was retained on reaction with thionyl chloride under conditions which are found [15] to result in the loss of the elements of methanol from a β-methoxy-acid.

The methoxyl group was removed by the action of acetic anhydride in the presence of toluene-*p*-sulphonic acid (cf. Huffmann and Lott [16]), followed by refluxing of the product (mixture of acetoxy-acid and -anhydride) with glacial acetic acid; this gave the acetoxy-acid, *O*-acetylmeromycolic acid, which on hydrolysis with benzene–methanolic potassium hydroxide afforded the hydroxy-acid, meromycolic acid. The infrared spectrum of the latter showed no γ-lactone-carbonyl absorption (1760 cm.$^{-1}$ region), indicating that the hydroxyl group is not in γ-position to the carboxyl group; hence the methoxyl group in *O*-methylmeromycolic acid must be beyond the γ-position. Further, since removal of

[8] Asselineau and Lederer, *Biochim. Biophys. Acta*, 1951, **7**, 126.
[9] Asselineau, *Bull. Soc. chim. France*, 1952, 557.
[10] Linstead, Owen, and Webb, *J.*, 1953, 1211.
[11] Pudles and Lederer, *Bull. Soc. Chim. biol.*, 1954, **36**, 759.
[12] Cf. Schlenk, *Annalen*, 1949, **565**, 204; Linstead and Whalley, *J.*, 1950, 2987; Skellon and Taylor, *J.*, 1953, 1433.
[13] Boast and Polgar, *J.*, 1957, 3800.
[14] Darzens and Levy, *Compt. rend.*, 1933, **196**, 348.
[15] Morgan and Polgar, unpublished work.
[16] Huffmann and Lott, *J. Biol. Chem.*, 1948, **172**, 789.

XUM

the methoxyl group did not lead to an unsaturated acid the methoxyl group was probably not attached to a tertiary carbon atom.

(I) $CH_3 \cdot [CH_2]_{n-1} \cdot CH{:}CH \cdot R \cdot CO_2Me$

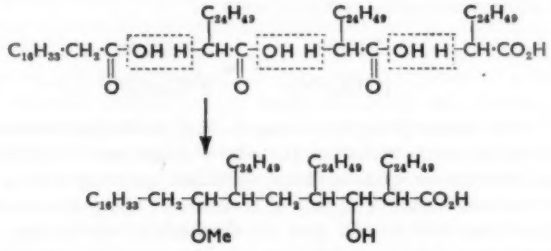
(II) $CH_3 \cdot [CH_2]_n \cdot CH(OX) \cdot R \cdot CO_2H$

(III) $CH_3 \cdot [CH_2]_n \cdot CH(OMe) \cdot R \cdot CH{:}C(CH_2]_{23} \cdot CH_3) \cdot CO_2H$

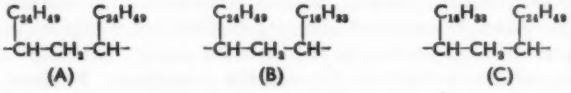
(IV) $CH_3 \cdot [CH_2]_n \cdot CH(OMe) \cdot R \cdot CH(OH) \cdot CH([CH_2]_{23} \cdot CH_3) \cdot CO_2H$

Pyrolysis of methyl *O*-acetylmeromycolate, followed by oxidation of the resulting unsaturated product, methyl anhydromeromycolate, gave a straight-chain acid, presumed to be heptadecanoic acid, together with the half-ester of a branched-chain dicarboxylic acid. Since pyrolysis of an acetate has been shown [17] to give only the least substituted olefin, with no rearrangement, methyl anhydromeromycolate may be formulated as (I), and *O*-acetylmeromycolic acid as (II; X = Ac), where *n* is probably 16, and R represents a branched-chain alkyl residue; meromycolic acid is then (II; X = H), and *O*-methylmeromycolic acid has structure (II; X = Me). Accordingly, the structures of anhydromycolic and mycolic acid are formulated as (III) and (IV), respectively.

The analytical figures obtained for some of the above degradation products agree better with a formula $C_{97}H_{194}O_4$ for mycolic acid than with the C_{88} formula proposed previously, but in view of the high molecular weight such formulæ are only an approximation; if a composition $C_{97}H_{194}O_4$ is assumed for mycolic acid, R in the above formulæ (I) to (IV) is $C_{51}H_{102}$. The structural features so far established point to a biogenesis of



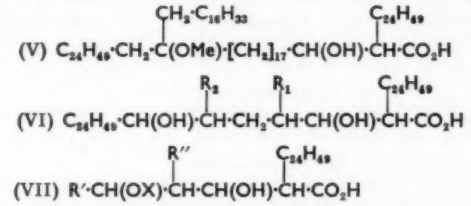
mycolic acid from hexacosanoic and stearic acid units,[18] with reduction of carbonyl groups to methylene or to the *sec.*-alcohol stage, and with or without *O*-methylation of the latter, as in the annexed scheme. On this hypothesis formulation of mycolic acid as (IV) where R is (A), (B), or (C) deserves consideration; the formula with R = (A) corresponds to a composition $C_{97}H_{194}O_4$, and those with R = (B) or (C) represent $C_{89}H_{178}O_4$.



Asselineau and Lederer, from studies of a complex mixture of hydroxy-, methoxy-, and unsaturated acids resulting on reaction of " α-mycolic acid " from the strain " Test " with acetic anhydride and potassium hydrogen sulphate, inferred structure (V) for the mycolic acid.[19] Asselineau proposed for " α_2-mycolic acid," isolated from the strain R_1 and

[17] Bailey and King, *J. Amer. Chem. Soc.*, 1955, **77**, 75.
[18] Cf. ref. 2, p. 213.
[19] Asselineau and Lederer, *Bull. Soc. chim. France*, 1953, 335.

regarded as having the composition $C_{87}H_{174}O_4$, the structure (VI) with the portion between the hydroxyl groups stated to be hypothetical.[20] Another structure was advanced by



Aebi, Vilkas, and Lederer[21] for the principal acid from the strain " Brévannes " which they suggested was a mixture of (VII; X = Me) and (VII; X = H), but it is difficult to reconcile these formulæ with the reported formation, by the action of acetic anhydride, of a diene-acid with only one double bond conjugated with the carboxyl group. Evidently, more chemical evidence is needed to clarify the position. This is also desirable in view of the recent controversy[22] on " cord factor " which has been claimed to be toxic and to consist of a trehalose ester of mycolic acid.[23]

Experimental

Ultraviolet spectra were determined for purified *cyclo*hexane solutions and infrared spectra for natural films or paraffin mulls. The alumina used for chromatography (Spence, type H) was acid-washed and activated at 110°, and its activity tested according to the method of Bröckmann and Schodder.[24] Petrol refers to light petroleum, b. p. 40—60°.

Isolation of Mycolic Acid.—The crude acid was obtained in earlier studies [5] from the *iso*propyl ether extract (B) of the bacterial cells. The methanol-insoluble product resulting from partial hydrolysis of the lipids was subjected to a more vigorous hydrolysis by refluxing benzene–methanolic potassium hydroxide for 215 hr. (cf. ref. 5). Addition of methanol to a benzene solution of the liberated acids precipitated crude mycolic acid, m. p. 52—54°. This acid (15 g.) was dissolved in hot benzene (90 c.c.) and filtered while warm; methanol (180 c.c.) was then added slowly with stirring, and next day the precipitated mycolic acid collected and washed with methanol. The product (14·5 g.) was a pale yellow powder, m. p. 54—55° (Found: C, 81·8; H, 13·8; OMe, 2·2. Calc. for $C_{97}H_{194}O_4$: C, 81·7; H, 13·7; OMe, 2·2. Calc. for $C_{89}H_{178}O_4$: C, 81·5; H, 13·6; OMe, 2·4%). The *amide*, prepared *via* the acetyl derivative by partial reduction of the crude acetylmycolamide with lithium aluminium hydride, had m. p. 73—75° (Found: C, 81·4; H, 13·7; N, 1·0. $C_{97}H_{195}O_3N$ requires C, 81·7; H, 13·8; N, 1·0%).

Mycolic acid, purified by the above procedure, was used for the degradation experiments described later. Five successive precipitations from benzene did not raise the m. p. above 54—55°. Fractional precipitation from benzene, by adding to purified mycolic acid (6 g.) in benzene (30 c.c.) 20-c.c. portions of methanol, gave fractions which all had m. p. 54—55°.

A portion (0·5 g.) of mycolic acid was chromatographed in petrol on alumina (10 g.; activity II). The following fractions were obtained: (i) 0·02 g., eluted by petrol–benzene (1 : 1), (ii) 0·03 g. eluted by ether, (iii) 0·33 g. eluted by ether–acetic acid (9 : 1), and (iv) 0·01 g. eluted by ether–acetic acid (4 : 1). The total amount recovered was 0·39 g. (78%), the main fraction (iii) having m. p. 54—55°.

Methyl mycolate (1·02 g.; obtained from the acid by means of diazomethane as a wax, m. p. 43—44·5°) gave on chromatography in petrol on alumina (35 g.; activity II) fractions: (i) 325 mg., eluted by petrol–benzene (3 : 1), (ii) 430 mg., eluted by petrol–benzene (1 : 1), (iii) 165 mg., eluted by benzene, and (iv) 65 mg., eluted by ether (97% recovery). Fractions (i) to (iii) were almost colourless products of m. p. 43—44·5° and appeared to be identical; fraction (iv) which

[20] Asselineau, *ibid.*, 1953, 427.
[21] Aebi, Vilkas, and Lederer, *ibid.*, 1954, 79.
[22] Spitznagel and Dubos, *J. Exp. Med.*, 1955, **101**, 291; Bloch, Defaye, Lederer, and Noll, *Biochim. Biophys. Acta*, 1957, **23**, 312.
[23] Noll, Bloch, Asselineau, and Lederer, *ibid.*, 1956, **20**, 299.
[24] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

was deep yellow melted at 40—41°, but its infrared spectrum was indistinguishable from that of methyl mycolate.

Pyrolysis of Mycolic Acid and its Derivatives.—Pyrolytic distillation of mycolic acid (3·2 g.) gave, in addition to higher-boiling material, a product (0·9 g.), b. p. 200—250° (bath)/0·1 mm., which after purification by formation of a urea complex crystallised from acetone as a white solid, m. p. 85—87° (Found: C, 78·5; H, 13·2. Calc. for $C_{26}H_{52}O_2$: C, 78·8; H, 13·2%). Francis and Piper [25] give m. p. 87·7° for hexacosanoic acid.

Mycolamide gave on pyrolytic distillation a product, b. p. 210—230° (bath)/0·07 mm., m. p. 110—111·5° (Found: C, 79·0; H, 13·2; N, 3·3. Calc. for $C_{26}H_{53}ON$: C, 79·0; H, 13·5; N, 3·5%). Marie [26] records m. p. 109° for cerotic amide.

On distillation of methyl mycolate (3 g.; prepared as stated above) (Found: C, 81·5; H, 13·4. Calc. for $C_{98}H_{196}O_4$: C, 81·8; H, 13·7%) two distinct fractions were obtained, *viz.*, (i) 0·8 g., b. p. 170—190° (bath)/0·06 mm., and (ii) 1·9 g., b. p. 300—360° (bath)/0·1 mm. Fraction (i), after purification *via* its urea complex and crystallisation from acetone, had m. p. 61·5—62° (Found: C, 79·0; H, 13·1. Calc. for $C_{27}H_{54}O_2$: C, 79·0; H, 13·2%); Francis and Piper [25] give m. p. 62·9° for methyl hexacosanoate. Fraction (ii) showed in its infrared spectrum a band at 1733 cm.$^{-1}$ which suggested the presence of some ester. A sample (1 g.) was hydrolysed by refluxing benzene–methanolic potassium hydroxide, and the product resulting on acidification chromatographed on alumina. Petrol eluted a white wax (0·85 g.), m. p. 36—40° (Found: C, 84·5; H, 13·8; OMe, 1·8%), which was not acidic (titration). The product which was obviously a mixture showed in its infrared spectrum a carbonyl band at 1695 cm.$^{-1}$. Ultraviolet light absorption: max. 2080 and 2300 Å (ε 4380 and 3420, respectively).

Anhydromycolic Acid (III).—Toluene-*p*-sulphonyl chloride (0·3 g.) (purified by shaking its benzene solution with aqueous sodium carbonate and by crystallisation from dry benzene) was added to a solution of methyl mycolate (0·5 g.) in dry pyridine (2 c.c.), and the mixture refluxed for 5 hr. Acidification of the product, followed by ether-extraction, gave the crude toluene-*p*-sulphonyl ester of methyl mycolate. This ester (0·4 g.) in benzene (10 c.c.) was refluxed with 5% methanolic potassium hydroxide (5 c.c.) for 6 hr.; the mixture was then acidified and extracted with ether. The product, m. p. 39—42° (Found: no S), was largely anhydromycolic acid (ultraviolet absorption: max. 2100 and 2180 Å; ε 12,000 and 12,700, respectively). Reaction with diazomethane gave methyl anhydromycolate (max. 2140 and 2200 Å; ε 11,900 and 11,420, respectively).

When methyl mycolate (0·6 g.) was refluxed with acetic anhydride (30 c.c.) and potassium hydrogen sulphate (3 g.; freshly fused) for 3 hr. (cf. ref. 8), the product showed in its infrared spectrum no band in the 1093 cm.$^{-1}$ region (alkyl ether), and the analytical values indicated the presence of two acetyl groups (Found: C, 80·3; H, 12·9. Calc. for $C_{101}H_{198}O_6$: C, 80·4; H, 13·2%).

Oxidation of Methyl Anhydromycolate.—Potassium permanganate was introduced continuously into a refluxing solution of methyl anhydromycolate (10 g.) in dry acetone (150 c.c.) with the aid of a Soxhlet extractor (the usual paper thimble was replaced by a wad of glass wool on which was placed 1 g. of powdered potassium permanganate). When the rate of oxidation became very slow (the pink colour persisted for 30 minutes' refluxing), the hot solution was filtered, and the manganese dioxide precipitate washed with hot acetone, then refluxed with dry ether (50 c.c.). After centrifuging of the cooled mixture for 0·5 hr. the ethereal solution was decanted; this prodecure was repeated twice with fresh portions of dry ether.

The combined acetone and ether filtrates were evaporated; examination of the residue (2·8 g.) by chromatography on alumina indicated that most of the material was methyl mycolate and anhydromycolate.

The manganese dioxide precipitate was dissolved by the addition of sodium hydrogen sulphite and dilute hydrochloric acid, and the mixture extracted with ether. Evaporation of the ethereal extract afforded a mixture of the acidic oxidation products. Preliminary studies of this material showed that chromatography on alumina gave no separation, the same mixture being eluted by 49 : 1 and 19 : 1 ether–acetic acid. Chromatography on silica (The British Drug Houses Ltd., " silica gel 30—120 mesh ") gave a number of fractions, but no distinct separation. Distillation of a sample (0·5 g.) gave two fractions, *viz.*, (i) b. p. 160—200° (bath)/0·02 mm., and (ii) b. p. 260—300° (bath)/0·02 mm. Fraction (i) was obtained as a

[25] Francis and Piper, *J. Amer. Chem. Soc.*, 1939, **61**, 577.
[26] Marie, *Ann. Chim. Phys.*, 1896, **7**, 208.

white solid (0·2 g.), m. p. 79°; it formed a urea complex. Fraction (ii) was a soft yellow wax (0·2 g.), m. p. 45—60°, which did not form a urea complex. Finally, the procedure described below was adopted.

Separation of the acidic oxidation products. The above mixture of acids (5·3 g.) was dissolved in light petroleum (b. p. 60—80°; 200 c.c.), and urea (6 g.), moistened with a few drops of methanol, added. The mixture was stirred and heated to boiling, then allowed to cool. The urea complex was filtered off and washed with light petroleum, then dissolved in water; the straight-chain acid separated as a white solid. The light petroleum filtrate and washings were combined, concentrated (to 200 c.c.), and treated again with urea (8 × 2 g.) as above, until no more straight-chain acid was removed. This procedure gave the normal-chain acid (1·76 g.), m. p. 71—73°, as a pure white solid. The branched-chain acid, recovered from the light petroleum solution, was a pale yellow wax (2·82 g.), m. p. 44—47°.

The normal-chain acid, after several crystallisations from acetone, had m. p. 76°. Further purification *via* the urea complex, followed by crystallisation from acetone, and finally from benzene gave the acid as plates, m. p. 78·5° (Found: C, 78·6; H, 13·0. Calc. for $C_{25}H_{50}O_2$: C, 78·4; H, 13·2%). Its infrared spectrum was identical with that of a sample of pentacosanoic acid, obtained by oxidation of methyl 2-oxohexacosanoate;[13] the band progressions in the region 1333—1176 cm.$^{-1}$ (cf. ref. 27) were identical, and differed from those of hexacosanoic acid (obtained by pyrolysis of mycolic acid), and of tetracosanoic acid (kindly provided by Dr. J. C. Smith).

The branched-chain acid, O-*methylmeromycolic acid*, had $[\alpha]_D^{20}$ +1·4° (*l.* 1; *c* 3·559 in $CHCl_3$), and melted, after crystallisation from acetone, at 45—47° to a clear plastic which suddenly became mobile at 60°. It distilled unchanged at 300—320° (bath)/0·06 mm. (Found: C, 82·0, 81·5; H, 13·3, 13·5; OMe, 2·7. $C_{71}H_{142}O_3$ requires C, 81·7; H, 13·7; OMe, 3·0%); it showed no high-intensity absorption in the ultraviolet region. Infrared absorption: bands at 1709 (CO) and 1093 cm.$^{-1}$ (alkyl ether).

The *amide* was prepared by refluxing *O*-methylmeromycolic acid (0·3 g.) in benzene (5 c.c.) with thionyl chloride (1·5 c.c.) for 3 hr.; the benzene and excess of thionyl chloride were removed by distillation, and the residual crude acid chloride taken up in a little dry ether, then poured on ice-cold aqueous ammonia. The product crystallised from acetone as a white solid, m. p. 64—70° (Found: C, 81·5; H, 13·5; N, 1·7. $C_{71}H_{143}O_2N$ requires C, 81·6; H, 13·8; N, 1·4%); its infrared spectrum contained a band at 1093 cm.$^{-1}$ (alkyl ether).

In another experiment, the acid chloride was prepared as above, and, after addition of a little ether, poured into water. The product was unchanged *O*-methylmeromycolic acid; it showed no high-intensity ultraviolet absorption, and the infrared spectrum indicated that the methoxyl group was intact.

Demethylation of O-*Methylmeromycolic Acid.*—*O*-Methylmeromycolic acid (1 g.) was refluxed with acetic anhydride (20 c.c.) and toluene-*p*-sulphonic acid (0·3 g.) for 0·5 hr. The mixture was extracted with ether, and the extract washed with water, then evaporated, leaving a dark yellow wax. Examination of the infrared spectrum showed the presence of acetyl, some free acid carbonyl, and also two anhydride bands at 1821 and 1754 cm.$^{-1}$, thus indicating that the product was a mixture of the acetoxy-acid and the acetoxy-anhydride. It was then refluxed with glacial acetic acid (20 c.c.) for 2 hr. to decompose the anhydride. The product was poured into water and extracted with ether. The ether layer, after being washed with water and dried ($MgSO_4$), was evaporated, to give O-*acetylmeromycolic acid* (II; X = Ac), m. p. 39—40° and 45° after crystallisation from acetone (Found: C, 80·9; H, 13·0. $C_{73}H_{142}O_4$ requires C, 80·7; H, 13·3%). Its infrared spectrum showed the absence of methoxyl and anhydride, and the presence of acid carbonyl (1709 cm.$^{-1}$) and acetyl (1739 and 1238 cm.$^{-1}$).

O-Acetylmeromycolic acid (0·1 g.) was refluxed with 5% benzene–methanolic (1 : 1) potassium hydroxide (20 c.c.) for 4 hr. Acidification and ether-extraction gave *meromycolic acid* (II; X = H) which crystallised from acetone as a white powder, m. p. 40° (Found: C, 81·5; H, 13·3. $C_{70}H_{140}O_3$ requires C, 81·6; H, 13·7%).

Pyrolysis of Methyl O-*Acetylmeromycolate and Oxidation of the Product.*—*O*-Acetylmeromycolic acid (0·7 g.) was converted, by reaction with diazomethane, into methyl *O*-acetylmeromycolate, m. p. 33—35°. This ester was pyrolysed by distillation at 300—400° (bath)/14 mm. The whole distilled, and the distillate was redistilled twice at the same pressure; a small charred residue remained. The distilled product was refluxed with acetone (50 c.c.) and powdered

[27] Jones, McKay, and Sinclair, *J. Amer. Chem. Soc.*, 1952, **74**, 2575.

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potassium permanganate until the rate of oxidation became very slow (8 hr.). The acid and the neutral fraction were then separated as described before. The neutral fraction was found to be unoxidised ester. The acid fraction (0·32 g.) gave on distillation two fractions, (*a*) b. p. 140—180° (bath)/0·05 mm., and (*b*) b. p. 200—300° (bath)/0·05 mm.; no residue remained.

Fraction (*a*) was treated in light petroleum (b. p. 60—80°) with urea, moistened with a little methanol. A complex was formed, decomposition of which with water gave the acid as a soft wax, crystallising from methanol as a fine powder, m. p. 52—53° (Found: C, 75·4; H, 12·4. Calc. for $C_{17}H_{34}O_2$: C, 75·4; H, 12·7%).

Fraction (*b*) did not form a urea complex; it was redistilled at 280—300° (bath)/0·02 mm., to give a soft, pale yellow wax, m. p. 30—35°. Its infrared spectrum showed an acid carbonyl band at 1709 cm.$^{-1}$, and an ester carbonyl as a shoulder on the former band at 1736 cm.$^{-1}$. The product was obtained in too small amounts for further studies.

In another experiment, meromycolic acid on distillation at 300—350°/0·05 mm. gave a product which contained some unsaturated material. It was oxidised with potassium permanganate as above, but no attempt was made to separate acid from neutral products, and the whole material was distilled. Fraction (i), a pale yellow wax, was collected at 140—200°/0·05 mm. Fraction (ii), collected at 220—320°/0·05 mm., crystallised from methanol as a white powder, m. p. 43—47°, and from analysis appeared to be a dicarboxylic acid (Found: C, 79·4; H, 12·5. $C_{54}H_{106}O_4$ requires C, 79·1; H, 13·0%); its infrared spectrum showed a normal acid carbonyl frequency at 1709 cm.$^{-1}$.

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Dyson Perrins Laboratory, Oxford University. [*Received, April 12th*, 1957.]

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747. *Biosynthesis of Polynucleotides. Part I. The Mode of Action of Ribonuclease.*

By G. R. Barker, M. D. Montague, R. J. Moss, and Margaret A. Parsons.

The enzymic conversion of nucleoside cyclic phosphates into nucleoside alkyl phosphates has been studied and it has been found that only primary alcohols react. It is demonstrated that the above type of reaction takes place simultaneously with the enzymic degradation of ribonucleic acid.

It is shown that the action of alkoxide ions on cyclic phosphates is analogous in certain respects to the action of ribonuclease and suggestions are made concerning the mechanism of the enzymic reaction. A nucleoside *iso*propyl phosphate differs in properties from the corresponding benzyl phosphate.

In this series of investigations it is proposed to study the processes whereby polynucleotides are formed and broken down *in vivo*. Chemical analogies are being sought for enzymic reactions involved, and syntheses of metabolic intermediates and their analogues are being undertaken. The present communication describes reactions catalysed by the enzyme ribonuclease; some of the results discussed have been briefly reported earlier.[1]

Ribonuclease is known to degrade ribopolynucleotides by converting pyrimidine nucleoside-3′ alkyl hydrogen phosphate residues into nucleoside-2′ : 3′ hydrogen phosphates which are subsequently hydrolysed to nucleoside-3′ dihydrogen phosphates.[2,3,4] These reactions, which may be represented by (I ⟶ II ⟶ III), take place when R and R′ are parts of a polynucleotide chain, or when R′ is hydrogen and R is a simple residue such as methyl, ethyl, or benzyl. In the simpler cases, moreover, the reverse reaction (II ⟶ I) has also been observed, and by this process both simple alkyl phosphates of nucleosides

[1] Barker and Parsons, *Chem. and Ind.*, 1955, 1009.
[2] Markham and Smith, *Biochem. J.*, 1952, **52**, 552.
[3] Brown and Todd, *J.*, 1953, 2040.
[4] Brown, Magrath, and Todd, *J.*, 1952, 2708.

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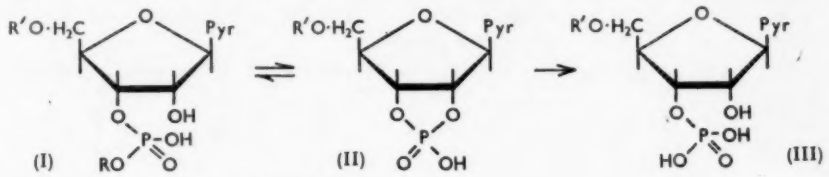
and dinucleoside monophosphates have been obtained enzymically.[4] In order to provide a basis for the synthesis of potential inhibitors of ribonuclease we have studied the structural requirements for the formation of alkyl phosphates by this reverse reaction of ribonuclease. The isolation and characterisation of each compound formed would have been impracticable



(Pyr = pyrimidinyl)

in a general survey of this kind, but the chromatographic behaviour of various types of nucleotide derivative is sufficiently well known to enable us to identify the nature of the products by this means.

The cyclic phosphate of uridylic acid was incubated with the enzyme and various alcohols; and, in control experiments, the cyclic phosphate was incubated with the enzyme alone, and with the alcohol alone. Several nucleoside alkyl phosphates have been described previously, and shown to have higher R_P values than the parent nucleotide or cyclic phosphate in propan-2-ol–ammonia–water.[3, 6, 7] By using this solvent system nucleoside alkyl phosphates formed in the reaction were detected readily. No fast-moving spot was observed in control experiments, but alkyl phosphates were detected after incubation of the cyclic phosphate with the enzyme and methanol, ethanol, propan-1-ol, butan-1-ol, or benzyl alcohol. Absorbing material was eluted from appropriate areas of the chromatograms and the optical densities of the eluates were measured at 260 mμ. Table 1 shows the R_P values and the approximate yields of the products.

TABLE 1. *Conversion of cyclic phosphates into alkyl esters by ribonuclease and by alkoxide ions.*

	Nucleotide ester			
	From uridine-2′ : 3′ hydrogen phosphate by ribonuclease		From adenosine-2′ : 3′ hydrogen phosphate by base-catalysis	
Alcohol	Yield (%)	R_P in solvent A	Yield (%)	R_P in solvent A
Methanol	15	0·40	51	0·44
Ethanol	19	0·46	45	0·48
Propan-1-ol	8	0·48	21	0·59
Butan-1-ol	7	0·53	44	0·68
Benzyl alcohol	10	0·55	36	0·68

To confirm that the fast-moving spots were in fact alkyl phosphates, the product from the incubation with ethanol was examined further. Both in the above solvent system and also in *iso*pentyl alcohol–5% sodium phosphate, it had the same R_P values as the ethyl phosphate formed as a by-product in the preparation of the cyclic phosphate. The R_P value was unchanged after treatment of the material with 0·1N-hydrochloric acid at 18° for 2 hours, whereas uridine-2′ : 3′ hydrogen phosphate was completely destroyed under these conditions. The material was converted into uridylic acid by prolonged treatment with ribonuclease. The progress with time of the enzyme-catalysed reaction between uridine-2′ : 3′ hydrogen phosphate and ethanol is shown in Table 2.

In contrast to the above results, no alkyl phosphates were detected after incubation of uridine-2′ : 3′ hydrogen phosphate with the enzyme and propan-2-ol, butan-2-ol, *tert.*-butyl alcohol, or phenol. The possibility was considered that these results were due either

[5] Heppel and Whitfeld, *Biochem. J.*, 1955, **60**, 1.
[6] Heppel, Whitfeld, and Markham, *ibid.*, 1955, **60**, 8.
[7] Dekker and Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3522.

to the inability of the chromatographic method to separate in these cases the alkyl (or aryl) phosphate from the cyclic phosphate, or to a rapid hydrolysis of the products to uridylic acid. Experiments described below rule out these possibilities for the reaction with propan-2-ol and it is therefore concluded that ribonuclease is able to catalyse the formation

TABLE 2. *Enzymic conversion of uridine-2′ : 3′ hydrogen phosphate into uridine ethyl phosphates.*

Time (hr.)	Uridylic acid (%)	Uridine-2′ : 3′ hydrogen phosphate (%)	Uridine ethyl phosphates (%)
0	20	80	0
2	40	57	3
3	46	47	7
3·75	48	39	13
4·5	52	32	16
5·5	57	24	19
20	100	0	0

of esters of nucleotides only with primary alcohols. The observation [6] that a 3′ : 5′-diester linkage is present in the enzymically produced dinucleoside monophosphate is in agreement with this conclusion.

The view had been expressed [7] that ribonuclease is concerned *in vivo*, not only with breakdown, but also with re-formation of ribopolynucleotides, and in agreement with this it has been recorded [8] that radioactive phosphorus is incorporated by certain tissues more rapidly into the dialysable fractions of ribonuclease digests of the tissue ribonucleic acids than into the non-dialysable "cores." The specificity we have observed would ensure the preservation of a 3′ : 5′-linked structure during re-synthesis of polynucleotides by by ribonuclease action. As far as we are aware, however, the reverse reaction (II ⟶ I) has only been observed with simple compounds and no direct evidence has been obtained that it does, in fact, take place concurrently with the degradation of polynucleotides by the enzyme. Important in this connection is the observation [9] that the degradation of ribonucleic acid by ribonuclease is inhibited by the nucleotides produced by alkaline degradation of the polynucleotide. It was considered that the enhanced reactivity of the enzyme towards freshly precipitated nucleic acid was the result of the elimination of nucleotides and small oligonucleotides during purification. Some doubt has been cast on the correct interpretation of these observations [10] and it was decided to investigate the problem further.

The activity of ribonuclease was measured by Kunitz's method [11] in which unchanged polynucleotide is precipitated by hydrochloric acid. Addition of mixtures of the 2′- and 3′-phosphate of adenosine, guanosine, cytidine, or uridine had no apparent effect on the activity of the enzyme measured by this method. This appears to be in contrast to Zittle's results,[9] but it is significant that he determined the activity of the enzyme by manometric measurement of carbon dioxide. This depends on the ability of the enzyme to liberate acidic dissociating groups, which takes place only in the second phase (II ⟶ III) of the degradation. On the other hand, Kunitz's method measures only the progress of the first phase of the reaction (I ⟶ II). We therefore examined the effect of nucleotides on the activity of ribonuclease as measured by continuous titration of acidic groups. The method used is essentially the same as that described by Edelhoch and Coleman.[12] They found that the activity of the enzyme, measured in this way, is reduced by the dialysable products of digestion. We examined the effects of various compounds of known structure and Edelhoch and Coleman's observations are consistent with our findings, outlined below. The enzyme was inhibited by the mixed 2′- and 3′-phosphates of adenosine, cytidine, and uridine, and by the nucleosides adenosine, cytidine, and uridine. No effect was observed

[8] Moldave and Heidelberger, *J. Amer. Chem. Soc.*, 1944, **76**, 679.
[9] Zittle, *J. Biol. Chem.*, 1946, **160**, 524.
[10] Cavalieri, *J. Amer. Chem. Soc.*, 1952, **74**, 1242.
[11] Kunitz, *J. Gen. Physiol.*, 1940, **24**, 15.
[12] Edelhoch and Coleman, *J. Biol. Chem.*, 1956, **219**, 351.

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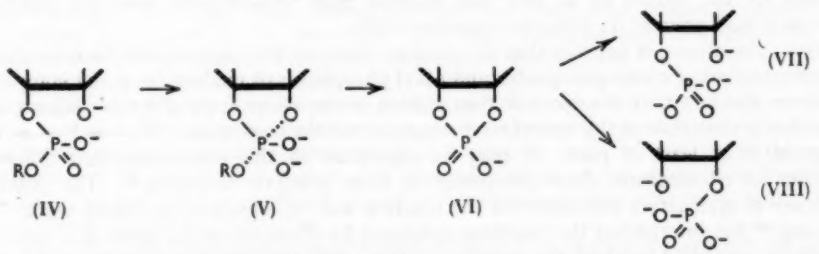
by adding the 5′-phosphate of adenosine, cytidine, or uridine. From these results we conclude that the inhibition observed by Zittle, by Edelhoch and Coleman, and by ourselves is due to suppression of the second phase (II ⟶ III) by reaction of the inhibitor with (II). Thus the nucleoside 5′-phosphates, being unable to react with (II) owing to the absence of a primary hydroxyl group, do not inhibit the enzyme. It thus appears that the reverse phase (II ⟶ I) can, in fact, take place during the action of ribonuclease on polynucleotides. It is interesting that Vandendriessche [13] has recorded that the two phases of the reactions catalysed by ribonuclease are affected to different degrees by certain inhibitors, but this effect cannot be related to our observations.

Apart from limitations imposed by the specificity of the enzyme, the reactions (I ⟶ II ⟶ III), catalysed by ribonuclease, are similar to those obtaining in the alkaline degradation of ribopolynucleotides.[3] We were interested to seek a chemical analogy of the reverse enzymic reaction (II ⟶ I), in order to throw light on the mechanism of the change. Two observations suggested that such an analogy might exist. First, that methyl phosphates of nucleosides are formed by interaction of the methoxide ion and ribopolynucleotides;[14] secondly, that potassium *tert.*-butoxide converts ribopolynucleotides largely into a mixture of cyclic phosphates.[15] In the first reaction, the alkoxide ion is believed initially to remove a proton from a sugar hydroxyl residue, thus promoting the formation of a cyclic phosphate, which is then attacked by the alkoxide ion, yielding an alkyl phosphate. The *tert.*-butoxide ion appears to be able to remove the proton from the sugar residue, but is unable to react with the cyclic phosphate formed. We therefore studied the action of various alkoxide ions on cyclic phosphates.

Adenosine-2′ : 3′ hydrogen phosphate, on treatment at room temperature with sodium methoxide (uridine-2′ : 3′ hydrogen phosphate behaved similarly with sodium methoxide), ethoxide, *n*-propoxide, *n*-butoxide, and benzyloxide, was largely converted into a mixture of the corresponding 2′- and 3′-alkyl phosphate (see Table 1). No alkyl phosphate was observed on chromatograms, however, with sodium *iso*propoxide or *tert.*-butoxide. In these instances the cyclic phosphate was recovered substantially unchanged apart from slight hydrolysis to adenylic acid. In order to test the sensitivity of the experimental procedure, the experiment with sodium *iso*propoxide was repeated on a larger scale. Elution of material from horizontal strips of the paper chromatogram indicated that not more than 2·5% of the cyclic phosphate had been converted into the *iso*propyl ester. It thus appeared possible that these reactions are analogous in mechanism to those catalysed by ribonuclease and it was decided to investigate this possibility further.



The suggestion has been made,[3] and supported by isotopic experiments,[16] that the alkaline hydrolysis of a compound such as (I) follows the course indicated by the partial structures (IV ⟶ V ⟶ VI ⟶ VII or VIII). A relatively stable intermediate was first postulated, but it is now thought that a transition-state complex such as (V) is concerned.[17]

[13] Vandendriessche, *Arch. Biochem. Biophys.*, 1956, **65**, 347.
[14] Lipkin and Dixon, *Science*, 1952, **116**, 525.
[15] Lipkin and Talbert, *Chem. and Ind.*, 1955, **143**.
[16] Lipkin, Talbert, and Cohn, *J. Amer. Chem. Soc.*, 1954, **76**, 2871.
[17] Brown, Magrath, Neilson, and Todd, *Nature*, 1956, **177**, 1124.

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It is immaterial to the present argument which view is correct, but it appears possible that a structure such as (V) may be involved, not only in the alkaline hydrolysis of (IV), but also in the reaction of an alkoxide ion with (VI). If so, the inability of (VI) to react with secondary or tertiary alkoxide ions may be due to steric resistance to the formation of (V). If this interpretation is correct, a compound (IV) in which R is secondary or tertiary should not show the lability to alkali which is characteristic of known compounds in which R is primary. Tener and Khorana [18] list the R_F value of the *iso*propyl esters of adenosine phosphates but give no further details of their properties. Using their method, we have prepared and characterised the mixed 2′- and 3′-*iso*propyl phosphate of uridine and have examined their behaviour towards alkali. As shown in Table 3, the material was hydrolysed by 0·5N-sodium hydroxide much more slowly than the corresponding benzyl esters. This supports the assumptions made above.

TABLE 3. *Hydrolysis of uridine-2′ and -3′* iso*propyl and benzyl phosphates.*

	Uridylic acid present (%)			
	Hydrolysis by sodium hydroxide		Hydrolysis by ribonuclease	
Time (hr.)	Pr^i ester	CH_2Ph ester	Pr^i ester	CH_2Ph ester
0·5	—	65	—	52
1	4	85	32	72
2	—	98	43	80
5	4	100	53	80
9	6	—	68	—
15	—	—	67	—

Since the reactions of cyclic phosphates with alkoxide ions and with alcohols in the presence of ribonuclease show some similarities, it seemed possible that an intermediate such as (V) might be concerned in the enzyme-catalysed reactions. If this were the case, the above *iso*propyl ester would be expected to resist degradation also by the enzyme. However, this was found not to be the case. In Table 3 are compared the rates of production by the enzyme of uridylic acid from the mixed 2′- and 3′-*iso*propyl phosphate of uridine and from the corresponding benzyl esters. In each case, only the 3′-ester would be expected to react. Although decomposition of the *iso*propyl ester is slower than that of the benzyl ester, appreciable quantities of uridylic acid are formed.

From these results it appears that whereas ribonuclease is unable to convert (II) into (I) when R′ is H and R is *iso*propyl, it is able to convert (I) into (II). This apparent anomaly may be due to the fact that the rate of conversion of (II) into (III) is not affected by the nature of R, and this reaction may predominate over the reaction (II ⟶ I) and prevent its detection experimentally.

From the above, it appears that the analogy between the enzyme and base-catalysed interconversions of cyclic phosphates and alkyl phosphates of nucleotides is not complete. However, the fact that the enzymic degradation of the above *iso*propyl ester takes place more slowly than that of the benzyl ester suggests that the mechanism (IV ⟶ V ⟶ VI) is operative at least in part. It may be significant in this connection that different fractions of ribonuclease show differences in their catalytic activities.[19] The possible existence of alternative pathways for the reaction will be considered in future work.

Long [20] has interpreted the reactions catalysed by ribonuclease in terms of a series of equations, according to which the enzyme combines with the phosphoryl residue of the substrate. Various groups in the enzyme molecule have been suggested as being concerned in the formation of such a complex, but no precise information is yet available. We believe that our results are in accord with the scheme envisaged by Long and we suggest tentatively a reason why ribonuclease catalyses the destruction or formation of only 3′-alkyl phosphates but not 2′-alkyl phosphates.

[18] Tener and Khorana, *J. Amer. Chem. Soc.*, 1955, **77**, 5349.
[19] Hakim, *Enzymologia*, 1956, **17**, 315.
[20] Long, *Science Progr.*, 1954, **42**, 266.

Heppel and Whitfeld [5] have shown that, provided an amino-group is present in the molecule, nucleoside-2′ phosphates and their esters have higher R_F values than the corresponding 3′-esters in the solvent system: saturated ammonium sulphate–propan-2-ol–M-sodium acetate (80 : 2 : 18 v/v/v). By this technique, and also using the *iso*pentyl alcohol–sodium phosphate system, we have separated the 2′- and 3′-alkyl phosphate

TABLE 4. *Proportions of isomeric alkyl phosphates formed by the action of alkoxide ions on adenosine-2′ : 3′ hydrogen phosphate.*

	2′-Alkyl phosphate			3′-Alkyl phosphate		
Catalytic base	R_F in B	R_F in C	%	R_F in B	R_F in C	%
Hydroxide	0·73	0·26	40	0·66	0·16	60
Methoxide	0·74	0·18	34	0·62	0·09	66
Ethoxide	0·77	0·25	32	0·68	0·11	68
n-Propoxide	0·76	0·19	25	0·62	0·06	75
n-Butoxide	0·75	0·13	25	0·63	0·05	75
Benzyloxide	0·66	0·11	20	0·56	0·02	80

produced by the action of alkoxide ions on adenosine-2′ : 3′ hydrogen phosphate. In Table 4 are given the relative proportions of each isomer formed. It is seen that the larger the attacking group, the higher is the proportion of 3′-ester. If it be assumed that an intermediate complex is formed in the enzymic reaction as suggested by Long [*e.g.*, (I; R′ = H, R = enzyme)], then by analogy with the above results it would be expected that such a complex would be formed only as in (I), and not by fission of the $C_{(3)}O{-}P$ bond. Further reaction of this complex with an alcohol would not be governed by the nature of the incoming residue and a 3′-ester would be formed in all cases as is, in fact, found in the enzyme-catalysed reactions.

EXPERIMENTAL

Paper chromatography was carried out with the following solvent systems: A, propan-2-ol–ammonia–water; [2] B, *iso*pentyl alcohol–5% sodium phosphate; [21] C, saturated ammonium sulphate–propan-2-ol–0·5M-sodium acetate; [2] D, butan-1-ol–acetic acid–water.[22]

Enzyme-catalysed Reaction of Uridine-2′ : 3′ Hydrogen Phosphate with Alcohols.—In a typical experiment, uridine-2′ : 3′ hydrogen phosphate (2·3 mg.) and ribonuclease (crystalline, protease-free enzyme) (5 mg.) in 2M-aqueous ethanol (0·5 c.c.) were brought to pH 7·5 by adding dilute aqueous ammonia. One drop of toluene was added and the solution was incubated at 37°. Aliquot parts were removed periodically and chromatographed by ascending development, with solvent system A, authentic samples of uridylic acid and the cyclic phosphate being chromatographed at the same time. Control solutions, from which either ethanol or ribonuclease was omitted were treated in the same way. Ultraviolet absorbing spots were cut from the paper and eluted with water, and the optical densities of the eluates at 260 mμ were measured. Table 2 shows the progress of the reaction with time. No material having an R_F value higher than that of the cyclic phosphate was observed in control experiments. In the main experiments, material eluted from the fast-moving spots was chromatographed again on the same paper as the uridine ethyl phosphate obtained as by-product in the preparation of the cyclic phosphate and had identical R_F values with this material in solvent systems A (0·46) and B (0·87). The material was unaffected as judged chromatographically after being treated with 0·1N-hydrochloric acid at 18° for 2 hr.

Other uridine alkyl phosphates were obtained as fast-moving spots (for R_F values and yields see Table 1) under similar conditions to those described above, 2M-methanol, 3M-propan-1-ol, 3M-butanol-1-ol, and 2M-benzyl alcohol being used. No products were detected from 3M-propan-2-ol, 3M-butan-2-ol, 3M-*tert.*-butyl alcohol, or 3M-phenol. In experiments with the higher alcohols, the cyclic phosphate was brought into solution by gentle warming.

Reactions of Cyclic Phosphates with Sodium Alkoxides.—The following general method was used. To adenosine-2′ : 3′ hydrogen phosphate (5 mg.) in the appropriate alcohol (0·4 c.c.), an approximately molar solution of the sodium alkoxide in the alcohol (0·1 c.c.) was added. The

[21] Carter, *J. Amer. Chem. Soc.*, 1950, **72**, 1466.
[22] Partridge, *Biochem. J.*, 1948, **42**, 238.

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solutions were kept in sealed tubes at room temperature for 20 hr. The solutions were then brought to pH 3·5 with aqueous acetic acid (2·5%, v/v) and chromatographed in solvent system A. The R_P values and the approximate yields, measured spectroscopically, of alkyl esters obtained from the cyclic phosphate of adenosine are shown in Table 1. The adenosine methyl phosphates are not as readily separated from the cyclic phosphate as are the other esters. In order to obtain the yield of the methyl phosphates, the material was eluted from the chromatogram and hydrolysed with 0·1N-hydrochloric acid at 18° for 2·5 hr. The solution was freeze-dried and the unchanged methyl phosphate was rechromatographed in solvent system A. Experiments showed that no measurable loss of the methyl phosphate was caused by the above treatment. No alkyl phosphates were observed under the above conditions when sodium *iso*propoxide or *tert.*-butoxide was used.

The mixed 2′- and 3′-alkyl phosphate obtained in the above experiments from papers developed with solvent system A were rechromatographed in solvent systems B and C. In each case two spots were observed and were separately eluted. The relative yields of isomers calculated from the optical densities of the eluates, measured at 260 mμ, are shown in Table 4.

Uridine-2′ : 3′ hydrogen phosphate (5 mg.) was treated with sodium methoxide, as described above except that the reaction time was 8 hr., and a spot was obtained on the chromatogram having the same R_P value (0·40) as the uridine methyl phosphate obtained in the enzymic reactions described above.

Uridine-2′ and -3′ iso*Propyl Hydrogen Phosphate.*—(*a*) To uridine-2′ : 3′ hydrogen phosphate (30 mg.) in propan-2-ol (1 c.c.) one drop of a saturated solution of hydrogen chloride in dioxan was added. After 10 min. the whole solution was applied to a sheet of Whatman filter paper (3MM) and irrigated with solvent system A. A component (R_P 0·48), travelling ahead of uridine and uridylic acid, was eluted with water and, after freeze-drying, yielded a material shown later to consist of a mixture of the ammonium salts of uridine-2′ and -3′ *iso*propyl hydrogen phosphate (Found: P, 8·1. Calc. for $C_{12}H_{22}O_9N_2P$: P, 8·1%).

(*b*) To uridine-2′ : 3′ hydrogen phosphate (120 mg.) in propan-2-ol (10 c.c.) was added a saturated solution of hydrogen chloride in dioxan (1 c.c.), and after 20 min. the solution was evaporated under reduced pressure to remove hydrogen chloride and brought to approx. pH 9 by adding dilute aqueous ammonia. Propan-2-ol was removed by extraction with ether. Excess of ether was removed under reduced pressure, the solution was diluted to approximately 2 l. and placed on a column (10 × 2·5 cm.) of Dowex-2 resin in the formate form. The column was eluted with a solution containing formic acid (0·01N) and ammonium formate (0·05N). A major component was eluted first and was shown by chromatography in solvent system A to contain the *iso*propyl ester. A small fraction containing the cyclic phosphate was eluted next, and uridylic acid was obtained by elution with ammonium formate (0·5N) and formic acid (0·5N). The solution containing the *iso*propyl ester was percolated through a column (10 × 1 cm.) of Amberlite IRC-50 resin in the hydrogen form, evaporated under reduced pressure, and finally freeze-dried, yielding a white hygroscopic powder (65 mg.). This was chromatographed in portions in solvent system A and the *ammonium salt* was eluted from appropriate areas of the paper and freeze-dried (Found: N, 11·02; P, 8·3. $C_{12}H_{22}O_9N_2P$ requires N, 10·9; P, 8·1%). Light absorption in H_2O: $\lambda_{max.}$ 261 mμ (ε9200), $\lambda_{min.}$ 231 mμ (ε 2700); in 0·01N-hydrochloric acid, $\lambda_{max.}$ 260 mμ (ε 9600), $\lambda_{min.}$ 230 mμ (ε 2300); in 0·01N-aqueous ammonia $\lambda_{max.}$ 260 mμ (ε 7100), $\lambda_{min.}$ 241 mμ (ε 5200). The material was not oxidised by sodium metaperiodate. In some experiments the ammonium salt was isolated by freeze-drying the eluate from the Dowex-2 resin, but in this case it was necessary to prepare the ammonium formate from ammonia and formic acid, since most samples of commercial ammonium formate contain traces of sodium formate. The *iso*propyl ester had R_P 0·6 in solvent system D; in solvent system B, complete separation from uridine-2′ and -3′ phosphates was not achieved.

Hydrolysis of Uridine-2′ and -3′ iso*Propyl Hydrogen Phosphate.*—(a) *By alkali.* The ester (3·1 mg.) was dissolved in 0·5N-sodium hydroxide (0·5 c.c.) and incubated at 37°. At intervals, aliquot parts were chromatographed in solvent system A, spots containing the *iso*propyl esters and uridylic acids were eluted with 0·1N-hydrochloric acid (5 c.c.) and the optical densities of the eluates at 260 mμ were measured. From these values, the percentage of the ester hydrolysed was calculated (see Table 3). The rate of hydrolysis of a mixture of uridine-2′ and -3′ benzyl hydrogen phosphate was measured in the same way.

(b) *By ribonuclease.* The ester (3·1 mg.) was dissolved in water (0·1 c.c.), and the solution was brought to pH 7·2 by adding dilute aqueous ammonia. Ribonuclease (10 μg.) in water

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(0·1 c.c.) was added and the mixture incubated at 37°. Samples were chromatographed at intervals, and the degree of hydrolysis was determined as described above (see Table 3). The experiments were repeated with a mixture of uridine-2′ and -3′ benzyl hydrogen phosphate.

(c) *By Russell's viper's venom.* The ester (2 mg.) in water (0·1 c.c.) was incubated at 37° for 2 hr. with the venom (0·4 mg.). Chromatography of the resulting solution showed that the ester had been completely destroyed, and that uridylic acid was the main product. After incubation under the same conditions for 20 hr., uridine was the sole product of the hydrolysis.

TABLE 5. *Measurement of ribonuclease activity by precipitation.*

	Optical density of supernatant liquid at 260 mμ				
	Acid added				
Time (min.)	None	Adenylic	Guanylic	Cytidylic	Uridylic
0·25	0·30	0·29	0·30	0·30	0·30
0·75	0·32	0·34	0·35	0·37	0·36
2	0·39	0·42	0·41	0·42	0·42
5	0·46	0·47	0·47	0·50	0·50
10	0·50	0·51	0·52	0·54	0·55
15	0·53	0·52	0·54	0·57	0·58
20	0·55	0·53	0·56	0·59	0·60
25	0·57	0·54	0·58	0·62	0·63
30	0·59	0·56	0·59	0·64	0·64
40	0·61	0·59	0·59	0·65	0·64
50	0·61	0·61	0·61	0·67	0·65
60	0·62	0·60	0·61	0·67	0·66

(d) *By acetic acid.* The ester (2 mg.) was heated at 100° for 2 hr. with 80% acetic acid (1 c.c.). On chromatography of the resulting solution, no *iso*propyl ester was detected. Uridylic acid and uridine were both present in appreciable quantities.

Measurement of the Activity of Ribonuclease.—(a) *By precipitation.* Yeast ribonucleic acid (Pharmaco-Chemical Products Co., Ltd.) (purified by precipitation with acetic acid [11]) (160 mg.) was dissolved in 0·1N-sodium acetate (10 c.c.). The nucleotide under test (160 mg.) was added and the mixture was brought to pH 7·6 by adding dilute aqueous sodium hydroxide. In blank experiments, the same procedure was adopted but without the addition of nucleotide. The solutions were kept at 25° and ribonuclease (0·3 mg.) in water (2 c.c.) was added. The solutions were quickly mixed, and at intervals aliquot parts (1 c.c.) were withdrawn, immediately added to N-hydrochloric acid (2 c.c.), and set aside for 2 min. The suspension was centrifuged, an aliquot part (1 c.c.) of the supernatant was diluted to 100 c.c. with water, and the optical density at 260 mμ was measured. In experiments with nucleotides, the optical density at zero time in a blank experiment carried out simultaneously was subtracted from the observed optical density at each time. The values, corrected in this way for the absorption due to added nucleotide, are shown in Table 5.

(b) *By titration.* Yeast ribonucleic acid (0·8 g.) was suspended in water (20 c.c.) and the pH was brought to 7·8 (Cambridge pH meter) by adding 0·05N-sodium hydroxide. Various quantities of the nucleotide or nucleotide under test were added and the pH was again adjusted to 7·8. In blank experiments the same procedure was adopted but no addition was made. Ribonuclease (0·6 mg.) in water (2 c.c.) was added and the pH kept at 7·8 by adding 0·05N-sodium hydroxide. During the first approx. 30 min. the consumption of alkali is linear with respect to time, and the uptake of alkali after a fixed interval of time, chosen within this range, is proportional to the concentration of enzyme. The ratios of the slopes of the plots of consumption of alkali against time in experiments with added materials and in blank runs give a measure of the inhibition of the enzyme. The following ratios of slopes were obtained: adenylic acid (mixed 2′- and 3′-phosphate), 0·69; cytidylic acid (mixed 2′- and 3′-phosphate), 0·55; uridylic acid (mixed 2′- and 3′-phosphate), 0·64; adenosine, 0·81; cytidine, 0·40; uridine, 0·59; adenosine-5′ phosphate, 0·98; cytidine-5′ phosphate, 0·95; uridine-5′ phosphate, 0·98.

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748. *Biosynthesis of Polynucleotides. Part II.* The Synthesis and Properties of Phosphoryl Derivatives of Adenine Glucoside.*

By G. R. Barker and G. E. Foll.

Syntheses of adenine glucoside-2′, -3′, -4′, and -6′ phosphate are described, and evidence is presented in support of the structures assigned. Adenine glucoside-4′ : 6′ hydrogen phosphate has been prepared and resembles other cyclic phosphates containing a six-membered ring. The -2′, -3′, and -4′ phosphate are not isomerised under conditions which bring about the interconversion of ribonucleoside-2′ and -3′ phosphates.

It is now established that cyclic phosphates of nucleosides are concerned in the chemical [1] and enzymic [2] degradation of ribopolynucleotides and it is also possible that they take part in the biosynthesis of polynucleotides by reversal of enzyme-catalysed degradations.[3,4] It seems reasonable to assume, therefore, that unnatural nucleotides which cannot yield cyclic phosphates or yield relatively stable cyclic phosphates, would be unable to take part in normal polynucleotide metabolism and might serve as a basis for the synthesis of metabolic blocking agents. The natural cyclic phosphates contain two fused five-membered rings and it is of interest to determine whether this ring system is essential to the normal functioning of polynucleotide synthesis and breakdown *in vivo*. With this object in view, we have synthesised the four isomeric phosphoric esters of 9-β-D-glucopyranosyladenine (adenine glucoside).

N^6 : $O^{6'}$-Dityrityl-9-β-D-glucopyranosyladenine was acetylated and, after removal of trityl groups, yielded crystalline 9-(2 : 3 : 4-tri-*O*-acetyl-β-D-glucopyranosyl)adenine. This compound was converted into the 6′-toluene-*p*-sulphonate which, with sodium iodide, yielded a syrup containing covalently bound iodine and considered to be essentially the 6′-iodo-derivative. The fact that covalently bound iodine is present confirms the assumption that the toluenesulphonyloxy-residue replaces the primary hydroxyl group and confirms the structure of the adenine triacetylglucoside. It is interesting that the formation of a *cyclo*nucleoside salt was not observed and we attribute this to the equatorial disposition of the 6′-substituent in the pyranosyl ring.

The adenine triacetylglucoside was phosphorylated by dibenzyl phosphorochloridate, and, after removal of protecting groups, yielded 9-β-D-glucopyranosyladenine-6′ dihydrogen phosphate, identified by the fact that it consumed 2 mols. of periodate with the liberation of 1 mol. of titratable acid. The same material was obtained as the sole product of the phosphorylation of adenine glucoside with phosphorus oxychloride in dry pyridine (cf. Part III [5]). Phosphorylation with phosphorus oxychloride in moist pyridine gave a mixture consisting mainly of the 6′-phosphate together with small quantities of other compounds which were not completely resolved by ion-exchange chromatography. Substantial amounts of the 2′-, 3′-, and 4′-phosphate were not formed, although phosphorylation of adenosine under similar conditions (see Part III [5]) gave appreciable quantities of the 2′- and 3′-phosphate. Newth [6] observed that toluenesulphonylation of an equatorial hydroxyl group takes place readily, as does formation of a carboxylic ester,[7] but this appears not to be the case with phosphorylation. This adds further weight to the

* Part I, preceding paper.

[1] Brown and Todd, *J.*, 1952, 52.
[2] Markham and Smith, *Biochem. J.*, 1952, **52**, 552.
[3] Heppel and Whitfield, *Biochem. J.*, 1955, **60**, 1; Heppel, Whitfield, and Markham, *ibid.*, p. 8.
[4] Barker and Parsons, *Chem. and Ind.*, 1955, 1009.
[5] Barker and Foll, following paper.
[6] Newth, *J.*, 1956, 441.
[7] de la Mare in Klyne's "Progress in Stereochemistry," Butterworths Ltd., London, 1954, Vol. I, p. 61.

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belief that the behaviour of adenosine is due to the favourable disposition of the 2′- and 3′-hydroxyl groups for cyclic phosphate formation. We were unable to identify a 4′ : 6′-cyclic phosphate amongst the products of phosphorylating adenine glucoside in moist pyridine but, owing to the small amount of material, resolution was not good enough for the presence of such a compound to be excluded.

Phosphorylation of N^6 : $O^{6'}$-ditrityl-9-β-D-glucopyranosyladenine in pyridine with dibenzyl phosphorochloridate gave a mixture which was separated by ion-exchange chromatography. Three large fractions were obtained which were eluted in the same region as the minor products of the phosphorylation of adenine glucoside in moist pyridine, but no peak corresponding to the 6′-phosphate was obtained. Of the three fractions, one was resistant to periodate and is designated 9-β-D-glucopyranosyladenine-3′ dihydrogen phosphate; the other two each consumed 1 mol. of periodate. In order to distinguish between the last two fractions, the following experiments were carried out.

Adenine glucoside was converted into what we assumed to be crystalline 9-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)adenine, the assumption being justified by experiments described below. Phosphorylation of this material yielded two nucleotides which were separated by ion-exchange chromatography. One proved to be the 3′-phosphate described above. The other was identical with one of the compounds obtained by phosphorylation of ditritylglucosyladenine. This nucleotide is designated 9-β-D-glucopyranosyladenine-2′ phosphate on the assumption of the structure of the benzylidene compound. No 6′-phosphate was obtained in this experiment. It follows that the benzylidene compound was substituted at position 6′ and one other, not position 3′, since the 3′-phosphate was obtained as described above. Thus the benzylidene derivative is either 9-(2 : 6-*O*-benzylidene- or 9-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)adenine, and we consider the former to be excluded on steric grounds. The benzylidene derivative was resistant to periodate, as are analogous compounds containing the same bicylic system.[8] We consider that the foregoing results justify the assumption of the structure of the benzylidene compound and therefore also the structures assigned to the nucleotides. The above 2′-phosphate had an R_F value which was lower than those of the other isomers in *iso*pentyl alcohol–sodium phosphate but higher than those of the others in *iso*butyric acid–ammonia. Although it is impossible to give a detailed explanation of this behaviour, it is believed to be connected with the proximity of the phosphate and nitrogenous residue in the 2′-ester. Whereas in adenosine-2′ phosphate these two residues are in true *trans*-positions relative to each other, in the glucoside derivative they almost certainly occupy equatorial positions which would allow of interactions between the groups.

Treatment of adenine glucoside with phenyl phosphorodichloridate gave 9-β-D-glucopyranosyladenine-4′ : 6′ phenyl phosphate. Like methyl α-D-glucopyranoside-4 : 6 phenyl phosphate,[9] the compound was resistant to periodate but, unlike the methyl glucoside cyclic phosphate, the adenine derivative could not be hydrogenated. It was hydrolysed by 80% acetic acid to syrupy 9-β-D-glucopyranosyladenine-4′ : 6′ hydrogen phosphate which was also obtained from the 6′-(dihydrogen phosphate) by treatment with trifluoroacetic anhydride. The properties of adenine glucoside-4′ : 6′ hydrogen phosphate resemble those of other cyclic phosphates containing a six-membered ring,[8,9,10] and, in agreement with this, interconversion of the 4′- and 6′-(dihydrogen phosphate) in acid solution was not observed. We have been unable to obtain any evidence of the formation of cyclic phosphates of adenine glucoside in which adjacent hydroxyl groups of the pyranosyl ring are esterified. Nor have we been able to effect interconversion of the 2′-, 3′- and 4′-phosphate of adenine glucoside with boiling 80% acetic acid or trifluoroacetic anhydride, under which conditions, ribonucleoside-2′ and -3′ phosphate are isomerised. It therefore appears unlikely that 2′-, 3′-, or 4′-phosphate of gluconucleosides could take part in

[8] Baddiley, Buchanan, and Szabo, *J.*, 1954, 3826.
[9] Baddiley and Thain, *J.*, 1952, 3783.
[10] Mosher, Reinhart, and Prosser, *J. Amer. Chem. Soc.*, 1953, **75**, 4899.

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reactions *in vivo* in which cyclic phosphates act as intermediates. We are attempting to verify this and to explore the possibility of using such compounds as antimetabolites.

Experimental

9-(2 : 3 : 4-*Tri*-O-*acetyl*-β-D-*glucopyranosyl*)*adenine*.—Triphenylmethyl chloride (1·9 g.) was added to adenine glucoside (prepared from N^6-acetylchloromercuripurine and tetra-*O*-acetyl-α-D-glucopyranosyl bromide by Davoll and Lowy's method [11]) (1 g.) in dry pyridine (15 c.c.) at room temperature, and the solution set aside for 7 days, or, in some experiments, heated at 100° for 3 hr. The cooled solution was poured into ice-water (200 c.c.), and saturated aqueous barium chloride was added dropwise to coagulate the precipitated $N^6 : O^{6'}$-ditrityl-9-β-D-glucopyranosyladenine which was collected, washed with water, and dried over phosphoric oxide. This material was heated at 100° with pyridine (10 c.c.) and acetic anhydride (5 c.c.) for 30 min., set aside overnight, and poured into cold water. The precipitate (3 g.) was collected, dried, and boiled for 30 min. with 80% acetic acid (50 c.c.). Triphenylmethyl acetate crystallised on cooling and was removed. The filtrate was poured into water and, after removal of the precipitate, the solvent was removed under reduced pressure. The residual 9-(2 : 3 : 4-*tri*-O-*acetyl*-β-D-*glucopyranosyl*)*adenine*, crystallised from ethanol, had m. p. 132° (Found : C, 47·8; H, 5·2; N, 16·5. $C_{17}H_{21}O_8N_5$ requires C, 48·2; H, 5·0; N, 16·55%).

Toluenesulphonylation of 9-(2 : 3 : 4-*Tri*-O-*acetyl*-β-D-*glucopyranosyl*)*adenine*.—A solution of toluene-*p*-sulphonyl chloride (0·2 g.) and 9-(2 : 3 : 4-tri-*O*-acetyl-β-D-glucopyranosyl)adenine (0·4 g.) in dry pyridine (15 c.c.) was set aside at room temperature for 2 days. Water (8 c.c.) was added followed by saturated aqueous sodium hydrogen carbonate (25 c.c.) at 0° and the solution was extracted with chloroform. The extract was washed successively with cold saturated sodium hydrogen sulphate (20 c.c.) and water (10 c.c.) and dried (Na_2SO_4). Removal of the solvent gave an amorphous solid which was heated at 100° in a sealed tube with acetone (10 c.c.) and sodium iodide (0·2 g.). Crystallisation of sodium toluene-*p*-sulphonate began after 10 min. and was complete in 1 hr. The solid was filtered off and the solvent removed under reduced pressure. The residue was dissolved in water (10 c.c.) and extracted with chloroform (2 × 10 c.c.). The combined extracts were washed with water (10 c.c.) and dried (Na_2SO_4). Removal of the solvent gave a syrup which contained iodine but gave no precipitate with aqueous silver nitrate.

9-β-D-*Glucopyranosyladenine*-6′ *Dihydrogen Phosphate*.—(a) *From* 9-(2 : 3 : 4-*tri*-O-*acetyl*-β-D-*glucopyranosyl*)*adenine*. To the starting material (1·3 g.) in dry pyridine (20 c.c.) at −40°, dibenzyl phosphorochloridate (from 2·5 g. dibenzyl phosphite) in pyridine (15 c.c.) was added with stirring during 3 hr. The solution was set aside at room temperature overnight. Water (10 c.c.) and sodium carbonate (1 g.) were added and the mixture was evaporated under reduced pressure to dryness. The residue was dissolved in chloroform (60 c.c.), the solution filtered, and the filtrate was washed with aqueous sodium carbonate and water and dried (Na_2SO_4). Chloroform was removed under reduced pressure and the residual gum was hydrogenated at room temperature in aqueous ethanol in presence of a mixture of palladium–charcoal and platinum black. The filtrate from the catalyst was evaporated to dryness under reduced pressure. The residue was dissolved in methanol (50 c.c.), methanolic ammonia (50 c.c., saturated at −10°) was added, and the solution set aside at 0° overnight. Removal of the solvent gave the ammonium salt of the nucleotide, chromatographically homogeneous in the *iso*pentyl alcohol–5% sodium phosphate system (See Table). An aqueous solution of the material was percolated through a column of Dowex-1 formate and eluted with formic acid. Removal of the solvent by evaporation and freeze-drying yielded 9-β-D-*glucopyranosyladenine*-6′ *dihydrogen phosphate* (Found : P, 8·3. $C_{11}H_{16}O_8N_5P$ requires P, 8·22%), which gave a *brucine salt* (Found : C, 53·2; H, 6·2; N, 9·55; P, 2·25. $C_{57}H_{68}O_{16}N_9P,7H_2O$ requires C, 53·0; H, 6·35; N, 9·76; P, 2·40%). On being oxidised with sodium metaperiodate, the nucleotide consumed 2·04 mols. of oxidant with the release of 1·1 mol. of titratable acid.

(b) *From adenine glucoside*. To adenine glucoside (dried at 100°/0·01 mm. for 24 hr.) (0·1 g.) in pyridine (dried with potassium hydroxide and by distillation twice from phosphoric oxide) (5 c.c.) at 0°, phosphorus oxychloride (redistilled immediately before use) (0·075 c.c.) in dry pyridine (0·5 c.c.) was added dropwise with stirring in the absence of atmospheric moisture.

[11] Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650.

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The solution was set aside at room temperature overnight, then cooled to −10°, and 50% aqueous pyridine was added. N-Sodium hydroxide equivalent to the chloride ions present was added and the solvent removed under reduced pressure. The residue was diluted with water to give an approximately 0·05M-solution with respect to phosphorus, and brought to pH 8 by adding aqueous sodium hydroxide. The solution was chromatographed on a column (5 × 15 cm.) of Dowex-1 formate and eluted as described by Cohn.[12] A single peak was obtained which, after evaporation and freeze-drying, yielded a material having the same R_P value as 9-β-D-glucopyranosyladenine-6′ dihydrogen phosphate in the *iso*pentyl alcohol–5% sodium phosphate system.

Phosphorylation of Ditritylglucosyladenine.—To the crude ditrityl glucosyl adenine described above (prepared from 0·15 g. of adenine glucoside) in pyridine (10 c.c.), phosphorus oxychloride (0·45 c.c.) in pyridine (4·5 c.c.) was added, followed by water (0·045 c.c.) in pyridine (0·45 c.c.). The solution was set aside overnight and 50% aqueous pyridine (5 c.c.) was added. The solution was poured into ice-water (50 c.c.) and saturated aqueous barium chloride was added to coagulate the precipitate which was collected by centrifuging and washed with water. The precipitate was boiled with 80% acetic acid (10 c.c.), triphenylmethyl acetate was removed by filtration of the cooled solution, and the filtrate was poured into water (50 c.c.) and filtered (charcoal). The filtrate was brought to pH 7·4 by addition of hot saturated aqueous barium hydroxide and, after removal of a slight precipitate, the solution was diluted to 1 l. and chromatographed on a column (1 × 10 cm.) of Dowex-1 formate. Three large well-resolved peaks were eluted with 0·1M-formic acid. Fractions were grouped, evaporated, and freeze-dried, giving respectively 9-β-D-glucopyranosyladenine-2′ dihydrogen phosphate which gave a *brucine salt*, m. p. 172—174° (Found: C, 53·3; H, 6·35; N, 9·45; P, 2·42. $C_{57}H_{66}O_{16}N_9P,7H_2O$ requires C, 52·99; H, 6·35; N, 9·76; P, 2·40%); 9-β-D-glucopyranosyladenine-3′ dihydrogen phosphate, which gave a *brucine salt*, m. p. 198—200° (Found: C, 53·1; H, 6·3; N, 9·6; P, 2·2%); 9-β-D-glucopyranosyladenine-4′ dihydrogen phosphate, which gave a *brucine salt*, m. p. 185—190° (Found: C, 53·0; H, 6·15; N, 9·5; P, 2·3%). R_P values are shown in the Table. The 2′- and 4′-dihydrogen phosphate each consumed 1 mol. of sodium metaperiodate; the 3′-dihydrogen phosphate was not oxidised.

R_P Values of derivatives of adenine glucoside.

Adenine glucoside derivative	*iso*Pentyl alcohol–5% sodium phosphate [13]	*iso*Butyric acid–ammonia [14]
Unsubstd.	0·62	0·77
-2′ Dihydrogen phosphate	0·53	0·84
-3′ Dihydrogen phosphate	0·72	0·63
-4′ Dihydrogen phosphate	0·68	0·58
-6′ Dihydrogen phosphate	0·60	0·76
-4′ : 6′ Hydrogen phosphate	0·60	0·91
-4′ : 6′ Phenyl phosphate	—	0·54

9-(4 : 6-O-*Benzylidene*-β-D-*glucopyranosyl*)*adenine.*—Adenine glucoside (1·25 g.), anhydrous zinc chloride (3 g.), and benzaldehyde (15 c.c.) were shaken together at room temperature for 24 hr. The resulting solution was added dropwise with vigorous stirring to ether (250 c.c.), and the solid was collected, washed with ether and dried. The dry solid was dissolved in Cellosolve (20 c.c.), sodium hydroxide (1·25 g.) in water (10 c.c.) was added, the mixture was set aside for 10 min., and carbon dioxide was passed through it until neutral to litmus and thereafter for 5 min. The precipitate was removed and washed with hot Cellosolve, and the combined filtrates were concentrated to 5 c.c. Water (25 c.c.) was added and the 9-(4 : 6-O-*benzylidene*-β-D-*glucopyranosyl*)*adenine* was collected, washed with a little water, and crystallised from aqueous ethanol (yield, 1 g.). It had m. p. 300—301° (Found: C, 56·05; H, 5·05; N, 18·2. $C_{18}H_{19}O_5N_5$ requires C, 56·1; H, 4·94; N, 18·18%). The material was not oxidised by sodium metaperiodate over a period of 3 days.

Phosphorylation of 9-(4 : 6-O-*Benzylidene*-β-D-*glucopyranosyl*)*adenine.*—The material (0·355 g.) was phosphorylated as described for ditritylglucosyladenine. After decomposition of excess of phosphorus oxychloride, the solution was neutralised with aqueous sodium carbonate and the solvents were removed under reduced pressure. The residue was dissolved in a little

[12] Cohn, *J. Amer. Chem. Soc.*, 1950, **72**, 1471.
[13] Carter, *J. Amer. Chem. Soc.*, 1950, **72**, 1466.
[14] Magasanik, Vischer, Doniger, Elson, and Chargaff, *J. Biol. Chem.*, 1950, **186**, 37.

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aqueous dioxan, and 30% aqueous acetic acid (40 c.c.) was added and the solution heated at 90° for 4 hr. The cooled solution was evaporated to dryness under reduced pressure, and the residue was dissolved in water, brought to pH 8 by adding saturated aqueous barium hydroxide, diluted to 2 l., and chromatographed as previously described on a column (3 × 20 cm.) of Dowex-1 formate. Materials from the two fractions obtained were isolated as described above and had R_P values (see Table) identical with the 2′- and 3′-phosphate respectively.

9-β-D-*Glucopyranosyladenine-4′ : 6′ Phenyl Phosphate.*—To adenine glucoside (0·67 g.) in dry pyridine (25 c.c.) phenyl phosphorodichloridate (0·48 g.) in dry pyridine (10 c.c.) was added dropwise with stirring at room temperature and the solution was set aside overnight. Water (25 c.c.) was added, and, after 2 hr. the solution was concentrated under reduced pressure and pyridine was largely removed by distillation with ethanol. The residue was dissolved in aqueous ethanol and percolated through a column of Amberlite IR-4B (OH form). Removal of the solvents from the eluate gave 9-β-D-*glucopyranosyladenine-4′ : 6′ phenyl phosphate* (0·35 g.) which crystallised from aqueous ethanol in needles, m. p. 272—275° (decomp.) (Found : C, 46·8; H, 4·25; P, 7·0. $C_{17}H_{18}O_7N_5P$ requires C, 46·9; H, 4·14; P, 7·1%).

9-β-D-*Glucopyranosyladenine-4′ : 6′ Hydrogen Phosphate.*—(*a*) The 4′ : 6′-(phenyl phosphate) described above (0·4 g.) was boiled with 80% acetic acid (25 c.c.) for 30 min. Acetic acid was removed by distillation with ethanol. The residue was dissolved in water, brought to pH 8, and chromatographed on Dowex-1 formate. The product from the main fraction was homogeneous on paper chromatograms (see Table) and travelled at approximately the same speed as adenosine-2′ : 3′ hydrogen phosphate on electrophoresis at pH 7·4. It was converted into the *barium salt* (Found : C, 31·6; H, 2·95; N, 16·3; P, 7·15. $C_{22}H_{26}O_{14}N_{10}P_2Ba$ requires C, 30·97; H, 3·04; N, 16·4; P, 7·27%).

(*b*) 9-β-D-Glucopyranosyladenine-6′ dihydrogen phosphate (0·05 g.) was set aside overnight at room temperature with trifluoroacetic anhydride (0·5 c.c.). Evaporation of trifluoroacetic anhydride gave a gum which was triturated with dry ether to yield a yellowish-white solid. This was set aside for 30 min. in saturated ethanolic ammonia (5 c.c.). The solution was evaporated to dryness, and the residue was washed with acetone and dissolved in water. It behaved on electrophoresis and paper chromatography in the same way as the material prepared from the 4′ : 6′-(phenyl phosphate).

THE UNIVERSITY, MANCHESTER. [*Received, October 1st,* 1956.]

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749. *Biosynthesis of Polynucleotides. Part III.* Selective Phosphorylation of Adenosine.*

By G. R. BARKER and G. E. FOLL.

EARLY attempts to use phosphorus oxychloride for the phosphorylation of adenosine did not result in useful preparative methods.[1,2] The low yields obtained were no doubt due partly to the inadequacy of the methods then available for isolation of the products. Although mixed nucleotides could not then be quantitatively analysed, the results suggested that the position of phosphorylation of unprotected adenosine depended on the conditions used : in dry pyridine, adenosine-5′ phosphate was believed to be formed,[1] whereas what is now presumed to have been a mixture of adenosine-2′ and -3′ phosphate was produced in aqueous barium hydroxide.[2]

The crude product obtained by interaction of adenosine and phosphorus oxychloride in presence of dry pyridine has now been chromatographed on Dowex-1 formate resin, elution being by 0·15M-formic acid.[3] Fractions corresponding to adenosine-5′, -2′, and

* Part II, preceding paper.

[1] Jachimowicz, *Biochem. Z.*, 1937, **292**, 356.
[2] Gulland and Barker, *J.*, 1942, 231.
[3] Cohn, *J. Amer. Chem. Soc.*, 1950, **72**, 1471.

-3′ phosphate were obtained (and identified by paper chromatography) in molecular proportions of **6 : 1 : 3**.

Phosphorylation with 1 mol. of phosphorus oxychloride and pyridine containing 0·1 mol. of water gave different results. In various experiments the addition of water followed or preceded the addition of phosphorus oxychloride, but in all cases chromatography of the crude product yielded the 5′-, 2′-, and 3′-phosphate in appreciable quantities, the molecular proportions being 1·5 : 1·75 : 1 and 1 : 2·7 : 2·5 under different experimental conditions.

Ion-exchange chromatography of the crude product obtained by phosphorylation in presence of aqueous barium hydroxide as previously described [2] yielded only two fractions. Under the conditions used, adenosine-5′, -2′, and -3′ phosphates are readily eluted separately in that order,[3] and since it is unlikely that the 2′-phosphate would be produced without any 3′-phosphate or *vice versa*, the appearance of only two fractions suggested the absence of the 5′-phosphate. This was confirmed by the fact that the mixed product suffered no dephosphorylation by the 5′-nucleotidase of Russell's viper's venom.[4] The molecular proportions of the 2′- and 3′-phosphate, calculated from the elution diagrams, were **6 : 4**.

It is thus confirmed that whereas in dry pyridine phosphorus oxychloride reacts preferentially with the primary hydroxyl group of adenosine, in aqueous barium hydroxide this hydroxyl group is not attacked; the use of moist pyridine gives results intermediate between the two extremes. In no experiment did the yield of nucleotide justify the use of the method preparatively. Viscontini and Bonetti [5] have pointed out that in the reaction of phosphorus oxychloride with water, the first compound to be formed is $HO{\cdot}POCl_2$, and, although no cyclic ester was recognised in the present experiments, it seems reasonable to assume that the formation of 2′- and 3′-phosphate in the presence of water is due to the reaction of the above dichloride with the possible initial formation of a cyclic phosphate. In dry pyridine, more complex products may be produced first [6] and these are less likely to be formed by reaction at the secondary hydroxyl groups for steric reasons.[7] Analogies with these selective phosphorylations are being sought among biological phosphorylations of nucleosides.

Experimental.—Phosphorylations in pyridine. To adenosine (dried at 100°/0·01 mm. for 24 hr.) (0·1 g.) in pyridine (dried with potassium hydroxide and by distillation twice from phosphoric oxide) (5 c.c.) at 0°, phosphorus oxychloride (redistilled immediately before use) (0·075 c.c.) in dry pyridine (0·5 c.c.) was added dropwise with stirring in the absence of atmospheric moisture. In some experiments, water (0·0075 c.c.) in pyridine (0·5 c.c.) was added either before or after the phosphorus oxychloride. The solution was set aside at room temperature overnight, then cooled to −10°, and 50% aqueous pyridine was added. N-Sodium hydroxide equivalent to the chloride ions present was added and the solvent removed under reduced pressure. The residue was dissolved in water and examined by paper chromatography. The bulk of the solution was brought to pH 8, diluted to give an approximately 0·05M-solution with respect to phosphorus, and percolated through a column (5 × 15 cm.) of Dowex-1 formate. The column was eluted as described by Cohn,[3] appropriate fractions were combined, and the concentration of nucleotide was determined spectroscopically. The solvent was removed under reduced pressure and finally by freeze-drying. Each fraction was identified by paper chromatography (Carter's method [8]). The yield of adenosine-5′ phosphate amounted to 4% in the experiments with dry pyridine.

Phosphorylation in aqueous barium hydroxide. Hydrated barium hydroxide (30 g.) was dissolved in hot water (25 c.c.), adenosine (1 g.) was added, and the solution vigorously shaken

[4] Gulland and Jackson, *Biochem. J.*, 1938, **32**, 597.
[5] Viscontini and Bonetti, *Helv. Chim. Acta*, 1951, **34**, 2435.
[6] Forrest and Todd, *J.*, 1950, 3295.
[7] Barker and Parsons, *Chem. and Ind.*, 1955, 1009; Barker, Montague, Moss, and Parsons, *J.*, 1957, 3786.
[8] Carter, *J. Amer. Chem. Soc.*, 1950, **72**, 1466.

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and cooled to 0°. Freshly distilled phosphorus oxychloride (1 c.c.) was added and shaking was continued, the temperature being kept below 10°. Two further quantities (1 c.c.) of phosphorus oxychloride were added, the temperature being brought to 0° before each addition. The mixture was diluted with water and freed from barium ions by adding N-sulphuric acid. Chloride ions were removed from the filtrate by addition of silver acetate and filtration, and the filtrate was adjusted to approximately pH 8 with 2N-sodium hydroxide. An aliquot part (75 c.c.) of the solution (1130 c.c.) was percolated through a column (1 × 10 cm.) of Dowex-1 formate and eluted as in the previous experiment, the two fractions being identified by paper chromatography. The yield of mixed nucleotides calculated from the spectroscopic measurements amounted to 14%. A further aliquot part (2 c.c.) was subjected to paper electrophoresis at pH 3·5 (citrate buffer) and 600 v. The paper was dried and examined in ultraviolet light.[9] A single spot was obtained and was eluted from the paper with water (3 × 10 c.c. at 90°). The combined eluates were concentrated under reduced pressure to 1 c.c. brought to pH 9 with 0·01N-sodium hydroxide, and incubated for 17 hr. at 37° with Russell's viper's venom (Ross Allen's Reptile Institute, Silver Spring, Florida) (1 mg.). The solution was then transferred to paper and subjected to electrophoresis as before. A single spot was again obtained and no material was observed in the region of the starting-line, indicating the absence of nucleoside.

THE UNIVERSITY, MANCHESTER. [*Received, October 1st*, 1956.]

[9] Holiday and Johnson, *Nature*, 1949, **163**, 216.

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750. *Methyl 2-Oxohexacosanoate.*

By N. G. BOAST and N. POLGAR.

IN connection with another investigation the keto-ester named above has been prepared by conversion of hexacosanoic acid into methyl 2-hydroxyhexacosanoate, and oxidation of the latter with chromium trioxide in glacial acetic acid.

The oxidation of methyl 2-oxohexacosanoate, by means of potassium permanganate in acetone, to pentacosanoic acid is also described.

Experimental.—Infrared spectra were determined for Nujol mulls.

Hexacosanoic acid. 13-Oxohexacosanoic acid was obtained from methyl 3-oxohexadecanoate [1] and methyl 11-iodoundecanoate (prepared as described [2] for the preparation of the corresponding ethyl ester) according to the general procedure given by Ställberg-Stenhagen and Stenhagen.[2] The keto-acid had m. p. 99·5° after crystallisation from glacial acetic acid (Found: C, 76·0; H, 12·2. Calc. for $C_{26}H_{50}O_3$: C, 76·0; H, 12·3%) (Stenhagen and von Sydow [3] record m. p. 98·1—98·3°). Reduction by refluxing the keto-acid (10·2 g.) with potassium hydroxide (17 g.), 90% hydrazine hydrate (19 c.c.), and triethylene glycol (52 c.c.) for 3·5 hr., followed by removal of water (until the temperature reached 198°), and further refluxing for 5 hr., gave on acidification hexacosanoic acid, m. p. 88° after crystallisation successively from benzene and glacial acetic acid (Found: C, 78·7; H, 13·3. Calc. for $C_{26}H_{52}O_2$: C, 78·7; H, 13·2%). Stenhagen and von Sydow [3] give m. p. 87·5°.

Methyl 2-hydroxyhexacosanoate. The procedure given by Mendel and Coops [4] for the lower homologues was followed. The crude product was chromatographed in light petroleum (b. p. 60—80°)–benzene (3 : 1) on alumina (activity I; Brockmann and Schodder [5]). Benzene–ether eluted *methyl 2-hydroxyhexacosanoate*, m. p. 79° (from ethanol) (Found: C, 76·3; H, 12·7. $C_{27}H_{54}O_3$ requires C, 76·0; H, 12·7%). Infrared absorption: bands at 3436 (OH) and 1721 cm.$^{-1}$ (CO).

Methyl 2-oxohexacosanoate. The hydroxy-ester (433 mg.) in glacial acetic acid (9 c.c.) was heated with a solution of chromium trioxide (77·5 mg.) in 50% aqueous acetic acid (1 c.c.) at 65° for 0·5 hr., then poured into water. The resulting *keto-ester* had m. p. 73° (from methanol)

[1] Ställberg-Stenhagen, *Arkiv Kemi, Mineralog. Geol.*, 1945, **20**, *A*, No. 19.
[2] Ställberg-Stenhagen and Stenhagen, *ibid.*, 1944, **19**, *A*, No. 1.
[3] Stenhagen and von Sydow, *Arkiv Kemi*, 1953, **6**, No. 29.
[4] Mendel and Coops, *Rec. Trav. chim.*, 1939, **58**, 1133.
[5] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

(Found: C, 76·0; H, 12·3. $C_{27}H_{52}O_3$ requires C, 76·3; H, 12·3%); its infrared spectrum showed carbonyl bands at 1742 and 1730 cm.$^{-1}$. The *oxime*, prepared by refluxing the keto-ester (0·05 g.) in benzene (0·5 c.c.) with hydroxylamine hydrochloride (0·1 g.) and sodium acetate (0·2 g.) in aqueous ethanol for 35 hr., had m. p. 101° [from light petroleum (b. p. 80—100°)] (Found: C, 74·1; H, 12·1; N, 3·6. $C_{27}H_{53}O_3N$ requires C, 73·8; H, 12·1; N, 3·2%).

Oxidation of the keto-ester. Powdered potassium permanganate was added to a boiling solution of methyl 2-oxohexacosanoate in dry acetone in small amounts at 10 min. intervals until the rate of oxidation became very slow. The product was pentacosanoic acid, m. p. 81·5° (from acetone) (Found: C, 78·3; H, 13·3. Calc. for $C_{25}H_{50}O_2$: C, 78·5; H, 13·2%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 7th*, 1957.]

751. *Some Methyl Ethers of Diosgenin.*

By W. J. PEAL.

THE preparation of the methyl 3 : 5-*cyclo*ethers of the sterols is one of the standard methods employed for the protection of these substances at the 3β-hydroxyl group and the 5 : 6-double bond during further reaction.[1,2,3]

Diosgenin toluene-*p*-sulphonate, when refluxed with dry methyl alcohol and anhydrous potassium acetate, gave 3 : 5-*cyclo*diosgenin methyl ether (6β-methoxy-3 : 5-*cyclo*-25*D*-spirostan), isolated as a gum, together with the normal methyl ether. The former ether was characterised by conversion into diosgenin chloride, diosgenin acetate, and diosgenin by standard methods.[2,3,4]

The molecular-rotation difference ($[M]_D$ of methyl 3 : 5-*cyclo*ether − $[M]_D$ of 3β-hydroxy-steroid) of +351° is in fair agreement with the figure of +364° obtained for various sterols.[2]

The normal methyl ether was prepared by refluxing diosgenin toluene-*p*-sulphonate with methyl alcohol and, secondly, by treating the potassium derivative of diosgenin with methyl iodide.

Experimental.—Light petroleum had b. p. 60—90°. $[\alpha]_D$ are in $CHCl_3$.

Diosgenin toluene-p-*sulphonate.* Diosgenin (3 g.) and toluene-*p*-sulphonyl chloride (3 g.) were left in dry pyridine (15 ml.) overnight. After dilution with water the product was extracted 3 times with ether, and the extract washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and concentrated, giving a gum which, after 3 crystallisations from acetone, had m. p. 155·5—156·5° (decomp.) or 158·5—159·5° (decomp.) (depending on rate of heating), $[\alpha]_D^{25}$ −94·0° (*c* 1·0) (Found: C, 71·7; H, 8·4. $C_{34}H_{48}O_5S$ requires C, 71·8; H, 8·5%).

Diosgenin methyl ether. (1) Diosgenin toluene-*p*-sulphonate (2·0 g.) was refluxed in methyl alcohol (200 ml.) for 2 hr. The solution was concentrated to 80 ml. and allowed to crystallise. Diosgenin methyl ether (m. p. 180—182°; 1·6 g.) was obtained which after two recrystallisations from methyl alcohol, had m. p. 180—182°, $[\alpha]_D^{25}$ −119° (*c* 0·5) (Found: C, 78·8; H, 10·3; OMe, 6·8. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·4; OMe, 7·25%).

(2) Diosgenin (1·0 g.) in dry benzene (30 ml.) was added to potassium (0·25 g.) emulsified under dry benzene (15 ml.). Methyl iodide (4 ml.) was added, the mixture refluxed for 4 hr., then methyl alcohol (1 ml.) added. The benzene solution was washed several times with water, dried (Na_2SO_4), and concentrated. The residual solid was chromatographed on alumina from light petroleum. Elution with light petroleum and light petroleum–benzene (20 : 1), and recrystallisation from methyl alcohol gave diosgenin methyl ether (0·75 g.), m. p. 180—182° (alone or mixed with the previous product), $[\alpha]_D^{25}$ −114° (*c* 1·2).

3 : 5-cyclo*Diosgenin methyl ether.* The toluene-*p*-sulphonate (3 g.) was refluxed for 6 hr. in dry methyl alcohol (300 ml.) containing anhydrous potassium acetate (3 g.). After methyl alcohol (200 ml.) had been distilled off under reduced pressure the solution was diluted with

[1] Fernholz **and Ruigh,** *J. Amer. Chem. Soc.*, 1940, **62**, 3346.
[2] Hey, Honeyman, and Peal, *J.*, 1952, 4836.
[3] Beynon, Heilbron, and Spring, *J.*, 1936, 907.
[4] Rees and Shoppee, *J.*, 1954, 3422.

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water and extracted with benzene. Concentration of the benzene extracts gave a gum (1·80 g.) which was chromatographed on alumina (60 g.) from light petroleum. Elution with light petroleum (5 × 100 ml.) gave a gum (0·79 g.), which after two recrystallisations from acetone had m. p. 88—89°, $[\alpha]_D^{25}$ −35° (*c* 0·6) (Found: C, 78·5; H, 10·4; OMe, 6·6. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·4; OMe, 7·25%). This substance is considered to be 3 : 5-cyclo*diosgenin methyl ether* from its specific rotation and from the rearrangement given below. Elution of the column with benzene–light petroleum (1 : 5) gave diosgenin methyl ether (0·09 g.) identified by m. p. and mixed m. p. Elution with benzene and benzene–chloroform mixtures gave unchanged diosgenin (0·20 g.), identified similarly.

Rearrangements of 3 : 5-cyclo*diosgenin methyl ether.* (*a*) The 3 : 5-*cyclo*ether (0·26 g.) was dissolved in acetic acid (10 ml.), and concentrated hydrochloric acid (0·4 ml.) was added. Needles of *diosgenin chloride* (0·21 g.) began to separate at once. After three recrystallisations from methyl alcohol–ethyl acetate they had m. p. 213—216°, $[\alpha]_D^{25}$ −109° (*c* 0·5) (Found: C, 74·4; H, 9·5; Cl, 8·6. $C_{27}H_{41}O_2Cl$ requires C, 74·8; H, 9·6; Cl, 8·2%). There was no depression (m. p. 214—216°) of mixed melting point with a sample prepared by the action of thionyl chloride on diosgenin.

(*b*) The 3 : 5-*cyclo*ether (0·18 g.) was refluxed for 5 hr. in acetic acid (10 ml.) containing freshly fused zinc acetate (1·0 g.). The acid solution was diluted and the product (0·18 g.) isolated in the usual way. After two recrystallisations from methyl alcohol–ethyl acetate the diosgenin acetate had m. p. and mixed m. p. 195—198°.

(*c*) The 3 : 5-*cyclo*ether (0·46 g.) in dioxan (50 ml.), water (20 ml.), and 2N-sulphuric acid (1 ml.) was left overnight, the mixture concentrated to 20 ml., and diluted with water, and the crude product was isolated in the usual way. Purification was by chromatography on alumina from benzene. Elution with benzene–chloroform (50 : 1) gave diosgenin (0·27 g.), m. p. and mixed m. p. 206—209° (from methyl alcohol–ethyl acetate).

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MAKERERE COLLEGE, KAMPALA, UGANDA. [*Received, February 18th,* 1957.]

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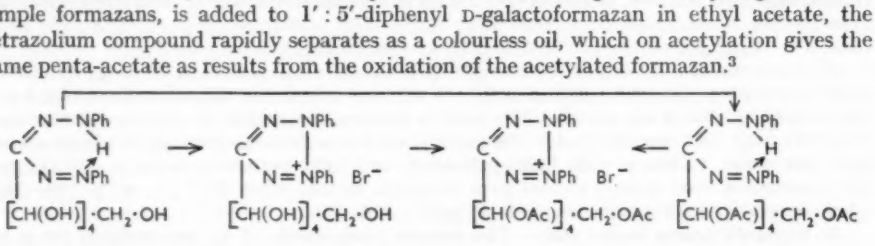
752. *Direct Conversion of Sugar Formazans into Tetrazolium Compounds.*

By L. MESTER and A. MESSMER.

TETRAZOLIUM derivatives of sugars have so far been prepared only by oxidation of acetylated sugar formazans and hydrolysis of the acetylated tetrazolium compounds so obtained.[1] Oxidation of the free sugar formazans with hydrochloric acid and pentyl nitrite or lead tetra-acetate failed to yield the products desired. It has now been found that, when *N*-bromosuccinimide, recommended by Kuhn and Münzing[2] for dehydrogenation of simple formazans, is added to 1′ : 5′-diphenyl D-galactoformazan in ethyl acetate, the tetrazolium compound rapidly separates as a colourless oil, which on acetylation gives the same penta-acetate as results from the oxidation of the acetylated formazan.[3]



Experimental.—Dehydrogenation of 1′ : 5′*-diphenyl-*D*-galacto-formazan with* N*-bromosuccinimide.* To the formazan (0·42 g.) in ethyl acetate (50 ml.), *N*-bromosuccinimide (0·5 g.) in ethyl acetate (25 ml.) was added at room temperature. In a few minutes the dark red solution

[1] Zemplén, Mester, and Eckhart, *Chem. Ber.*, 1953, **86**, 472.
[2] Kuhn and Münzing, *ibid.*, p. 858.
[3] Zemplén, Mester, Messmer, and Eckhart, *Acta Chim. Acad. Sci. Hung.*, 1952, **2**, 25.

changed to pale yellow and the tetrazolium compound separated as a pale yellow oil (0·41 g., 81%), $[\alpha]_D^{20}$ +19·1° (in EtOH). To this tetrazolium compound, pyridine (5 ml.) and acetic anhydride (3 ml.) were added. After 24 hr. at room temperature crystals were observed and ethyl acetate (8 ml.) was added. Crystallisation from absolute alcohol gave pale yellow needles (0·3 g.), m. p. 233—234°, $[\alpha]_D^{20}$ +43·5° (in EtOH), not depressed in m. p. on admixture with the acetate described below.

*Dehydrogenation of penta-*O*-acetyl-*1′ : 5′*-diphenyl-*D*-galactoformazan with* N*-bromosuccinimide.* To the formazan acetate (3·0 g.) in ethyl acetate (50 ml.) an equivalent amount of *N*-bromosuccinimide in ethyl acetate (140 ml.) was added at room temperature. In a few minutes the dark red solution changed to pale yellow. In 10 min. 5-galacto-*penta-acetoxypentyl*-2 : 3-*diphenyltetrazolium bromide* (4·0 g.) separated which, crystallised from absolute ethanol, had m. p. 233—234°, $[\alpha]_D^{20}$ +57·7° (in EtOH) (1·8 g.) (Found : N, 8·4; Ac, 32·0. $C_{35}H_{31}O_{10}N_4Br$ requires N, 8·45; Ac, 32·4%).

We thank Miss Ilona Batta for the microanalyses.

INSTITUTE OF ORGANIC CHEMISTRY,
TECHNICAL INSTITUTE OF BUDAPEST, HUNGARY. [*Received, March 18th*, 1957.]

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753. *The Interaction of Iron and Cobalt Nitrosyl Carbonyls with Triaryl Phosphites and Triaryl-phosphines, -arsines, and -stibines.*

By L. MALATESTA and A. ARÀNEO.

IT is known that carbon monoxide in nickel tetracarbonyl can be partially or completely replaced by ligands containing tervalent phosphorus as a donor atom, giving products of the type $Ni(PCl_3)_4$, $Ni(CO)\{P(OEt)_3\}_3$, and $Ni(CO)_2(Ph_3P)_2$ which, in general, are more stable than nickel carbonyl itself.[1,2]

Tricarbonylnitrosylcobalt, $Co(CO)_3(NO)$, and dicarbonyldinitrosyliron, $Fe(CO)_2(NO)_2$, are not only isosteric, but also have a distribution of effective charge very similar to that in nickel carbonyl. This had been deduced by one of us on the basis of considerations of electronegativities of the atoms in these complexes,[3] and has now been confirmed experimentally by the measurement of the electric dipole moments.[4]

The above considerations suggested the possibility that carbon monoxide in the nitrosyl carbonyls could be replaced by tervalent phosphorus donors as happens in nickel tetracarbonyl. As mentioned in a preliminary communication [5] these substitutions occur fairly smoothly. The products are listed in the Table.

Compound	M. p.	Colour	Compound	M. p.	Colour
$Fe(NO)_2(Ph_3P)_2$	194°	Brown	$Co(NO)(CO)\{(PhO)_3P\}_3$	86°	Yellow
$Fe(NO)_2\{(PhO)_3P\}_2$	62—72	Orange	$Co(NO)(CO)_2\{(p\text{-}C_6H_4Me)_3As\}$	*ca.* 125 *	Orange-red
$Fe(NO)_2(CO)(Ph_3As)$	100—110 *	Red			
$Fe(NO)_2(CO)\{(p\text{-}C_6H_4Me)_3As\}$	*ca.* 130 *	Red	$Co(NO)(CO)_2\{(p\text{-}C_6H_4Cl)_3As\}$	*ca.* 135 *	Red
$Fe(NO)_2(CO)(Ph_3Sb)$	105—115 *	Orange-red	$Co(NO)(CO)_2(Ph_3Sb)$	100	Red
			$Co(NO)(CO)_2\{(p\text{-}C_6H_4Me)_3Sb\}$	*ca.* 135 *	Red
$Fe(NO)_2(CO)\{(p\text{-}C_6H_4Me)_3Sb\}$	*ca.* 110 *	Red	$Co(NO)(CO)_2\{(p\text{-}C_6H_4Cl)_3Sb\}$	*ca.* 150 *	Red
$Co(NO)(CO)(Ph_3P)_2$	130	Red			

* Decomp.

We could not obtain cobalt derivatives in which all three molecules of carbon monoxide were replaced; even using an excess of triphenyl phosphite, which with nickel tetracarbonyl gives the compound $Ni(CO)\{(PhO)_3P\}_3$,[2] does not replace more than two carbon monoxide molecules from $Co(CO)_3(NO)$. This could be due to the weaker positive charge on the nitrosyl group bound to a metal, compared with carbon monoxide, which would make

[1] Wilkinson, *J. Amer. Chem. Soc.*, 1951, **73**, 5501.
[2] Malatesta and Sacco, *Ann. Chim.* (*Italy*), 1954, **44**, 134.
[3] Malatesta, *Gazzetta*, 1953, **83**, 964.
[4] Weiss, *Z. anorg. Chem.*, 1956, **277**, 221.
[5] Malatesta and Aràneo, *Rend. Accad. Naz. Lincei*, 1956, VIII, **20**, 365.

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further substitution of the carbon monoxide by the phosphorus ligand more difficult. The latter ligand carries an appreciable positive charge in its co-ordination compounds of this type, as shown by the magnitude of their electric dipole moments.

Tertiary aromatic phosphines replace two molecules of carbon monoxide in $Co(CO)_3(NO)$ and $Fe(CO)_2(NO)_2$, as they do in $Ni(CO)_4$, while tertiary aromatic arsines and stibines appear to be able to replace only one molecule of carbon monoxide in all cases.

The colour of the substitution products of tricarbonylnitrosylcobalt with triarylphosphites, -phosphines, -arsines, and -stibines ranges from yellow to brick-red. These products are all stable to air in the crystalline state, and also fairly stable in solution, in which they are monomeric. The solids are diamagnetic. The pure compounds can be obtained either by reprecipitation of a benzene solution with methanol, or by preparing the product in alcohol.

The iron derivatives, which are slightly more coloured than the corresponding cobalt compounds, are almost all less stable than their cobalt and nickel analogues, and are oxidised spontaneously in air when not perfectly dry and stored at low temperatures. They can be recrystallised from organic solvents and are diamagnetic and monomeric in solution.

Experimental.—Before the analyses the complexes were destroyed with concentrated sulphuric acid and potassium sulphate. The iron was determined oxidimetrically with permanganate, phosphorus as $Mg_2P_2O_7$, and nitrogen by Dumas's method on a semimicro-scale.

Molecular weights were determined cryoscopically in 2% benzene solution; the magnetic susceptibilities were measured by the Gouy method.

Dinitrosylbis(triphenylphosphine)iron. A concentrated toluene solution of triphenylphosphine (5·2 g.) was added to finely powdered $Fe(NO)_2(CO)_2$ (1·7 g.) in an inert atmosphere. After 6—8 hr., when gas evolution had ceased, an equal volume of cold absolute methanol was added, and the crystalline *product* (3·5 g.) filtered off and washed with methanol (Found: N, 4·35; P, 9·7; Fe, 8·75%; *M*, 635. $C_{36}H_{30}O_2N_2P_2Fe$ requires N, 4·4; P, 9·7; Fe, 8·8%; *M*, 640); it had χ_M -340×10^{-6}.

Dinitrosylbis(triphenyl phosphite)iron was prepared and purified as above from $Fe(NO)_2(CO)_2$ (1·7 g.) and triphenyl phosphite (6·2 g.) (yield, 2·5 g.) (Found: N, 3·9; P, 8·7; Fe, 7·7. $C_{36}H_{30}O_8N_2P_2Fe$ requires N, 3·8; P, 8·4; Fe, 7·6%). It is less stable than its triphenylphosphine analogue.

Carbonyldinitrosyltriphenylarsineiron. A saturated solution of triphenylarsine (3 g.) in toluene was added to $Fe(NO)_2(CO)_2$ (1·7 g.) under nitrogen. There was lively gas evolution and crystals of product began to separate. After 30 min., before the reaction was complete, the solid was filtered off in a nitrogen atmosphere and washed with cold absolute ethanol (yield, 2 g.). This *compound* had χ_M -215×10^{-6} and decomposed in air within a few days (Found: N, 6·35; As, 16·3; Fe, 12·7. $C_{19}H_{15}O_3N_2AsFe$ requires N, 6·2; As, 16·7; Fe, 12·4%).

The following compounds were prepared and purified as the arsine derivative from stoicheiometric amounts of reactants (1·7 g. of nitrosylcarbonyl):

*Carbonyldinitrosyltri-*p*-tolylarsineiron*, stable in air for a few days (yield, 2 g.) (Found: N, 5·6; As, 15·0; Fe, 11·6. $C_{22}H_{21}O_3N_2AsFe$ requires N, 5·7; As, 15·2; Fe, 11·4%).

Carbonyldinitrosyltriphenylstibineiron, stable in air only for a few hours (yield, 1·2 g.) (Found: N, 5·7; Sb, 24·4; Fe, 11·3. $C_{19}H_{15}O_3N_2FeSb$ requires N, 5·6; Sb, 24·4; Fe, 11·2%).

*Carbonyldinitrosyltri-*p*-tolylstibineiron* (yield, 2 g.) (Found: N, 5·3; Sb, 22·5; Fe, 10·5. $C_{22}H_{21}O_3N_2FeSb$ requires N, 5·2; Sb, 22·6; Fe, 10·4%).

Carbonylnitrosylbis(triphenylphosphine)cobalt, prepared and purified analogously to the corresponding iron compound from $Co(CO)_3(NO)$ (1·7 g.) and triphenylphosphine (5·2 g.) (yield, 3·5 g.) (Found: N, 2·2; P, 10·2; Co, 9·1%; *M*, 690. $C_{37}H_{30}O_2NP_2Co$ requires N, 2·2; P, 9·9; Co, 9·2%; *M*, 641).

Similarly prepared [from $Co(CO)_3(NO)$ (1·7 g.) and the stoicheiometric amount of ligand] were:

Carbonylnitrosylbis(triphenyl phosphite)cobalt (yield, 5 g.) (Found: N, 2·0; P, 8·6; Co, 8·0. $C_{37}H_{30}O_8NP_2Co$ requires N, 1·9; P, 8·4; Co, 8·0%), χ_M -420×10^{-6}.

Dicarbonylnitrosyltri-p-tolylarsinecobalt (yield, 4 g.) (Found: N, 2·9; As, 14·9; Co, 11·6. $C_{22}H_{21}O_3NAsCo$ requires N, 2·8; As, 15·2; Co, 12·0%).

Dicarbonylnitrosyltri-p-chlorophenylarsinecobalt (yield, 3·5 g.) (Found: N, 2·6; As, 13·3; Co, 10·0. $C_{20}H_{12}O_3NCl_3AsCo$ requires N, 2·5; As, 13·5; Co, 10·4%).

Dicarbonylnitrosyltriphenylstibinecobalt (yield, 3·5 g.) (Found: N, 2·9; Sb, 24·5; Co, 11·6. $C_{20}H_{15}O_3NCoSb$ requires N, 2·8; Sb, 24·5; Co, 11·85%).

Dicarbonylnitrosyltri-p-tolylstibinecobalt (yield, 3 g.) (Found: N, 2·6; Sb, 22·8; Co, 10·7%; *M*, 544. $C_{23}H_{21}O_3NCoSb$ requires N, 2·6; Sb, 22·5; Co, 10·9%; *M*, 540).

Dicarbonylnitrosyltri-p-chlorophenylstibinecobalt (yield, 4 g.) (Found: N, 2·4; Sb, 20·6; Co, 9·4. $C_{20}H_{12}O_3NCl_3CoSb$ requires N, 2·3; Sb, 20·2; Co, 9·7%).

The present work was supported by a grant from the Italian Research Council.

THE UNIVERSITY, MILAN. [*Received, March 25th*, 1957.]

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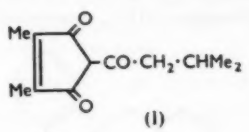
754. β-*Triketones. Part IV.* The Chromophore of Calythrone.*

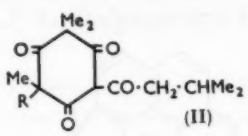
By A. J. BIRCH and R. J. ENGLISH.

THE formula (I) was assigned to calythrone [1] chiefly on the basis of published work,[2] and the formula was considered [3] to be supported by an examination of spectra. However, no models containing the chromophore of structure (I) appear to have been made and we have accordingly synthesised one for comparison.

Attempts to condense dimethylmaleic anhydride or ester with ketones in the presence of sodium ethoxide, sodium amide, or boron trifluoride failed to produce the desired triketones.[4] Another possible route is based on the suggested biosynthesis [3] of calythrone. This would involve the conversion of the *cyclo*hexanetrione (II; R = H) into the triketo-alcohol (II; R = OH) and then by the action of alkali into the *cyclo*pentane derivative (III; R = R′ = Me, R″ = Bu^t), followed by dehydration to calythrone (I). However, 3 : 3 : 5-trimethylphloracetophenone was not oxidised with oxygen and lead acetate as in the reaction employed in the analogous humulone series.[5] This type of reaction is known to fail or to give very poor yields in some cases.



(I)



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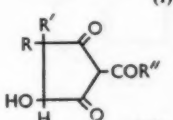

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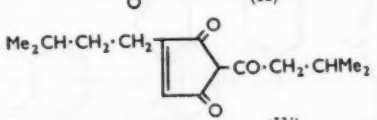

(IV)

At this stage, through the kindness of Dr. S. David (Nancy), we obtained access to dihydrohumulinic acid (III; R = H, R′ = CH_2Bu^t, R″ = Bu^t), dehydration of which with polyphosphoric acid gave the compound (IV), whose ultraviolet absorption [$\lambda_{max.}$ 240, 266 mμ (log ε 4·22, 4·26)] is very similar to that [3] of calythrone [$\lambda_{max.}$ 240, 266 mμ (log ε 4·29, 4·26)]. The infrared spectrum also is similar to that of calythrone in the region 1700—1600 cm.$^{-1}$ (in CS_2). There is a sharp peak at 1710 cm.$^{-1}$, presumably due to an

* Part III, Birch and Elliott, *Austral. J. Chem.*, 1956, **9**, 238.

[1] Birch, *J.*, 1951, 3026.
[2] Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286.
[3] Birch and Elliott, *Austral. J. Chem.*, 1956, **9**, 95.
[4] Birch and Murray, unpublished work.
[5] Campbell and Coppinger, *J. Amer. Chem. Soc.*, 1951, **73**, 1849.

XUM

αβ-unsaturated ketone grouping in a five-membered ring; this band is observable in the spectrum of dihydrohumulinic acid. A broad peak at 1620 cm.$^{-1}$ extending below 1500 cm.$^{-1}$ is present in both and appears to be characteristic of β-triketones of this type. Dihydrohumulinic acid has two bands in the hydroxyl region, 3560 and 3450 cm.$^{-1}$, the latter of which is missing from the spectrum of (IV).

It is notable that dihydrohumulinic acid is soluble in bicarbonate solutions, whereas the triketone (IV) is soluble only in carbonate solutions, to give a yellow salt.

Experimental.—*4-3′-Methylbutyl-2-isovaleroylcyclopent-4-ene-1 : 3-dione.*—Dihydrohumulinic acid (100 mg.) in a mixture of phosphoric acid (*d* 1·75; 4 c.c.) and phosphoric oxide (4 g.) was heated at 130° for 8 min. The *product* obtained by dilution with water, ether-extraction, and crystallisation from ether–pentane, had m. p. 75—76° (40 mg.) (Found: C, 72·0; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). It gave a deep brownish-red colour with alcoholic ferric chloride. Refluxing with powdered cupric acetate in methanol, dilution with water, and ether-extraction gave the copper salt as a greenish-yellow solid, m. p. 145—147° (from benzene).

We are indebted to the Cumberland Educational Committee for a grant (to R. J. E.).

THE UNIVERSITY OF MANCHESTER. [*Received, April 14th,* 1957.]

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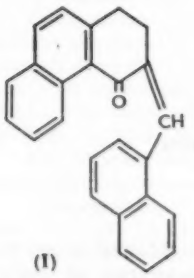
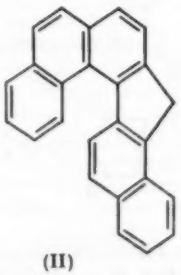
755. *A Synthesis of* 7 : 8-*Benzonaphtho*(2′ : 1′-3 : 4)*fluorene.*

By NG. PH. BUU-HOÏ and G. SAINT-RUF.

SEVERAL years ago, Buu-Hoï and Cagniant showed that the application of the Rapson–Shuttleworth cyclodehydration reaction[1] to 2-naphthylidene derivatives of 1-tetralone and more complex ketones afforded a convenient route to several condensed polycyclic fluorenes.[2] In those studies, the cyclodehydration of 1 : 2 : 3 : 4-tetrahydro-3-1′-naphthylmethylene-4-oxophenanthrene (I) was investigated and a hydrocarbon, m. p. 285°, isolated and assigned the tentative structure of 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene (II). This hydrocarbon, unknown at that time, was later prepared by Campbell from dimerisation products of β-2-naphthylpropiolic acid,[3] and found to melt at 138—139°. This led us to re-investigate the constitution of the hydrocarbon, m. p. 285°, which now proved to be the isomeric 7 : 8-benzonaphtho(1′ : 2′-3 : 4)fluorene (III), previously prepared by



(I)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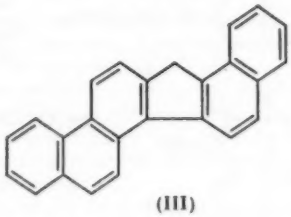
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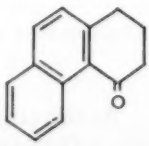

(IV)

Buu-Hoï and Cagniant.[4] This result could be explained by assuming either that a rearrangement occurred during the cyclodehydration of (I), as in the synthesis of 1 : 2 : 5 : 6-dibenzofluorene,[4] or that the starting ketone (IV) contained some of the isomeric 1-ketone if the recorded method[5] for the separation of β-1- and β-2-naphthoylpropionic acid is insufficient. The latter was found to be the case, as the pure 4-ketone obtained from

[1] Rapson and Shuttleworth, *J.*, 1940, 636.
[2] Buu-Hoï and Cagniant, *Rev. Sci.*, 1942, **80**, 319.
[3] Campbell, *J.*, 1954, 3659.
[4] Buu-Hoï and Cagniant, *Rev. Sci.*, 1942, **80**, 384; 1943, **81**, 30.
[5] Haworth, *J.*, 1932, 1125.

γ-2-naphthylbutyric acid which had been prepared by a malonic synthesis *via* pure 2-β-naphthylethanol [6] gave, with 1-naphthaldehyde, the condensation product of (I) with a melting point substantially higher than that previously recorded. Cyclodehydration of this product afforded, in good yield, 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene (m. p. 147°, higher than that recorded by Campbell, but giving the same absorption spectrum and the same dipicrate). This observation offers a convenient route to this difficultly accessible hydrocarbon (II), whose carcinogenic activity is being determined. Cyclodehydration of a sample of compound (I) prepared from the 4-ketone (IV) *via* a sample of γ-2-naphthylbutyric acid obtained according to the literature,[5] gave small amounts of hydrocarbon (III), together with the isomeric hydrocarbon (II).

Experimental.—1 : 2 : 3 : 4-*Tetrahydro*-3-1′-*naphthylmethylene*-4-*oxophenanthrene* (I). 1 : 2 : 3 : 4-Tetrahydro-4-oxophenanthrene (7 g.; m. p. 69°), prepared by cyclisation of pure α-2-naphthylbutyric acid, m. p. 99° (lit.,[5] m. p. 95—96°), with sulphuric acid, was shaken with α-naphthaldehyde (5·6 g.) in ethanol (50 c.c.) and a few drops of 30% concentrated aqueous potassium hydroxide and left overnight at room temperature. The solid precipitate formed was recrystallised twice from ethanol, giving pale yellow prisms (6 g.), m. p. 173° (Found: C, 89·7; H, 5·4. Calc. for $C_{25}H_{18}O$: C, 89·8; H, 5·4%). The product similarly prepared from impure ketone melted at 152—153° with sintering, and could not be purified further.

Cyclodehydration. A solution of the ketone (I) (5·5 g.; m. p. 173°) in anhydrous xylene (100 c.c.) was refluxed with finely powdered phosphoric oxide (4 g.) for 30 hr. After cooling, the dark violet mixture was poured into water (500 c.c.), the xylene solution washed with dilute aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent removed and the residue distilled *in vacuo*. The portion, b. p. 285—290°/0·4 mm., which did not solidify, was taken up in benzene and converted into a dipicrate, which formed brown-red needles, m. p. 175°, from benzene (lit.,[3] m. p. 175—176°). Decomposition of this with aqueous ammonia yielded 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene (II), leaflets (1 g.), m. p. 147° (from ethanol–benzene) (Found: C, 94·7; H, 5·2. Calc. for $C_{25}H_{16}$: C, 94·9: H, 5·1%); Campbell [3] gave m. p. 138—139°.

Cyclodehydration of a sample of compound (I) prepared from impure material yielded, after the usual treatment, a resinous distillate which was triturated with *cyclo*hexane; the small amount of solid obtained (0·1 g.) was recrystallised from benzene, giving needles, m. p. 286—287°, of 7 : 8-benzonaphtho(1′ : 2′-3 : 4)fluorene (III). The portion dissolved in *cyclo*hexane was freed from solvent and treated with a benzene solution of picric acid, giving the dipicrate (1·2 g.) of hydrocarbon (II). Both the condensed fluorenes gave intense violet fluorescence in benzene solution.

THE RADIUM INSTITUTE, THE UNIVERSITY OF PARIS. [*Received, April 15th*, 1957.]

[6] Karrer, Geiger, Ruegger, and Schwab, *Helv. Chim. Acta*, 1940, **23**, 585; Sontag, *Ann. Chim.*, 1934, **1**, 359.

756. *Some Aromatic Aldehydes.*

By KENNETH CLARKE.

SEVERAL disubstituted benzaldehydes were required as intermediates in another investigation. Preparation of di-*ortho*-substituted aldehydes proved extremely difficult, especially if one or both of the substituents were electron-attracting. Oxidation of the corresponding toluenes failed completely or gave very poor yields. The Sommelet reaction fails [1,2] with both di-*ortho*-substituted benzyl halides and also with benzyl halides substituted by more than one electron-attracting group.[3] Hass and Bender's reaction,[4] whereby aldehydes are obtained from benzyl halides after condensation with nitropropane, also fails for nitrobenzaldehydes.[3]

[1] Angyal, Morris, Rassack, and Waterer, *J.*, 1949, 2704.
[2] Fuson and Denton, *J. Amer. Chem. Soc.*, 1941, **63**, 654.
[3] Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141.
[4] Hass and Bender, *J. Amer. Chem. Soc.*, 1949, **69**, 1767.

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Kröhnke's method,[5] however, proved more satisfactory. This involves the preparation, from the requisite benzyl bromide, of the quaternary 1-benzylpyridinium salt, which with *NN*-dimethyl-*p*-nitrosoaniline will give a nitrone that can be split by mineral acid, thus forming the required aldehyde.

$$Ph{\cdot}CH_2Br \longrightarrow PhCH_2{\cdot}\overset{+}{N}C_5H_5\ Br^- \longrightarrow Ph{\cdot}CH{:}N(O){\cdot}C_6H_4{\cdot}NMe_2 \longrightarrow Ph{\cdot}CHO$$

By this method 2 : 6-dinitro- (58%), 2 : 6-dichloro- (50%), 2-nitro-4- (57%), and -6-chloro- (75%), and 2-bromo-6-nitro-benzaldehydes (79%) have been prepared in the overall yields given in parentheses. The three monofluoro-benzaldehydes were obtained in yields of only 15—20%; consequently the method has no advantage over those already available for these compounds.

Experimental.—*1-(2-Bromo-6-nitrobenzyl)pyridinium bromide.* Bromine (3 ml.) was added during 1 hr. to 2-bromo-6-nitrotoluene at 170°; the mixture was then illuminated (2 × 200 w) and the temperature maintained at 170° until the bromine had disappeared (2—3 hr.). Pyridine (7 ml.) and ethanol (10—15 ml.) were added to the cooled mixture, which was then heated for 1 hr. on a steam-bath. Cooling and recrystallisation (ethanol) gave the salt (16 g.) as prisms, m. p. 210°.

*2-Bromo-6-nitrophenyl-*N*-p-dimethylaminophenylnitrone.* N-Sodium hydroxide (60 ml.) was gradually added at 0° to a stirred suspension of 1-(2-bromo-6-nitrobenzyl)pyridinium bromide (8·0 g.) and *NN*-dimethyl-*p*-nitrosoaniline (4·0 g.) in ethanol (100 ml.), stirring was then continued for 2—3 hr., and the solution finally diluted. The precipitated nitrone was washed and crystallised (ethyl acetate), giving red-brown prisms (6·5 g.), m. p. 162°.

2-Bromo-6-nitrobenzaldehyde. The nitrone (10 g.) was heated for 5 min. with 6N-sulphuric acid (150 ml.) on a steam-bath. When recrystallised (from ethanol) the aldehyde formed pale yellow prisms (6·1 g.), m. p. 82°.

Compounds detailed in the Table were produced similarly.

Compound R	R′	M. p.	Solv.	Formula	Found, % C	H	N	Reqd., % C	H	N
Benzylpyridinium bromides, $RR'C_6H_3{\cdot}CH_2{\cdot}N^+C_5H_5\ Br^-$										
2 : 6-Cl_2		220°	EtOH	$C_{12}H_8NCl_2Br$	45·5	3·15	4·1	45·2	3·1	4·4
2 : 6-$(NO_2)_2$		166	[a]	$C_{12}H_{10}O_4N_3Br$	41·8	3·3	12·3	42·4	2·9	12·4
2-Cl : 6-NO_2		192	,,	$C_{12}H_9O_2N_2ClBr$	43·9	3·3	8·2	43·7	3·0	8·5
4-Cl : 2-NO_2		203	,,	,,	43·9	3·2	8·4	,,	,,	,,
2-Br : 6-NO_2		210	,,	$C_{12}H_9O_2N_2Br_2$	38·6	2·6	7·4	38·6	2·4	7·5
2-F, H		136	[b] $COMe_2$	$C_{12}H_{11}NBrF$	—	—	—	—	—	—
3-F, H		148	,,	,,	53·6	4·1	—	53·7	4·1	—
4-F, H		57—58	[c] $COMe_2$ +EtOH	,,	—	—	—	—	—	—
Nitrones, $RR'C_6H_3{\cdot}CH{:}N(O){\cdot}C_6H_4Me_2$										
2 : 6-Cl_2		156	[d] EtAc	$C_{15}H_{14}ON_2Cl_2$	58·0	4·5	—	58·3	4·5	—
2 : 6-$(NO_2)_2$		184	,,	$C_{15}H_{14}O_5N_4$	54·2	4·1	16·7	54·3	4·2	17·0
2-Cl : 6-NO_2		165	,,	$C_{15}H_{14}O_3N_2Cl$	56·1	4·6	13·1	56·3	4·4	13·1
4-Cl : 2-NO_2		166	,,	,,	56·6	4·6	—	,,	,,	,,
2-Br : 6-NO_2		162	,,	$C_{15}H_{14}O_3N_2Br$	49·6	3·8	—	49·5	3·9	—
2-F, H		83	EtOH	$C_{15}H_{15}ON_2F$	—	—	10·8	—	—	10·9
3-F, H		100	,,	,,	—	—	10·9	—	—	,,
4-F, H		127	,,	,,	—	—	10·7	—	—	,,

[a] *Perchlorate,* m. p. 174° (Found: C, 40·4; H, 2·8; N, 11·4. $C_{12}H_{10}O_8N_2Cl$ requires C, 40·1; H, 2·8; N, 11·7%). [b] *Perchlorate,* m. p. 100° (Found: C, 49·9; H, 4·1. $C_{12}H_{11}O_4NClF$ requires C, 50·1; H, 3·8%). [c] *Perchlorate,* m. p. 96° (Found: C, 49·8; H, 4·1%).

[d] The method described above gave only a low yield. Yields were, however, satisfactory when the reaction mixture was kept overnight with sodium ethoxide.

The author thanks Imperial Chemical Industries Limited for a grant.

THE UNIVERSITY, HULL. [*Received, 16th April,* 1957.]

[5] Kröhnke and Borner, *Ber.*, 1936, **69**, 2006; 1938, **71**, 2583.

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